The Synthesis and Evaluation of Pironetin and Pironetin Analogs as Ovarian Cancer Chemotherapeutic Agents

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Dedication

This thesis is dedicated to my parents Dee-Hua Huang and Chung-hwa Huang

Abstract

Pironetin is a natural product with potent antiproliferative activity against various cancer cell lines including ovarian cancer. Pironetin is proposed to inhibit cell division via formation of a covalent adduct with α-tubulin. The disruption of microtubule polymerization dynamics via binding to α-tubulin is a novel mechanism of action since current chemotherapeutics that target tubulin bind β-tubulin. α-Tubulin is an attractive target for ovarian cancer since the overexpression of the α-tubulin isoform TUBAC3 has been reported to be a predictor for short-term survival in ovarian cancer patients who did not respond to platinum/paclitaxel chemotherapy.

While pironetin displays potent *in vitro* activity, it had poor efficacy in a previous in vivo study in mice bearing P388 murine leukemia cells. Animals treated with pironetin also suffered from severe weight loss. To evaluate if pironetin would be a good candidate to develop as a chemotherapeutic agent, we evaluated the natural product's pharmacological properties. The natural product was found to have poor metabolic stability and form covalent adducts with other proteins and/or biomolecules containing a reactive thiol. We hypothesized these properties were the cause of the natural product's poor *in vivo* efficacy in the previous study. We therefore decided to synthesize pironetin analogs to improve upon the natural product's pharmacological properties and explore the SAR at different parts of the molecule.

We evaluated the SAR at the α,β-unsaturated lactone of pironetin, which is involved in the binding between pironetin and α-tubulin. We found that modifying the different stereocenters of the α,β-unsaturated lactone resulted in a loss of biological

activity. We also explored the addition of a functional group at the α-position of the α,β-unsaturated lactone to decrease off-target covalent adduct formation. The functionalization at this position resulted in a 100-1000 fold decrease in biological activity. We also evaluated the SAR of the substituent at the γ-position of the α,β-unsaturated lactone in pironetin. We found that groups with similar steric properties as the ethyl group in the natural product are tolerated at this position.

Along with evaluating the SAR at positions of the α,β-unsaturated lactone in pironetin, we also synthesized an analog to potentially improve upon the natural product's metabolic stability. We exchanged the non-conjugated olefin in the natural product, which is the primary site of metabolism, with a phenyl group. The phenyl-containing analog has similar antiproliferative activity as the natural product, but did not have improved metabolic stability. We have identified additional sites of metabolism of pironetin and the phenyl-containing analog that will need to be modified to improve upon the natural product's metabolic stability.

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List of Schemes

Compounds Index

List of Abbreviations

α	alpha
β	beta
γ	gamma
δ	delta
Å	angstrom
[Ox]	oxidation
Ac	acetyl
ADME	adsorption, distribution, metabolism, and excretion
Asn	asparagine
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
brsm	based on recovered starting material
Bu	butyl
^{i}Bu	isobutyl
^{t}Bu	*tert*-butyl
calc	calculated
cat.	catalytic
CRO	contract research organization
Cy	cyclohexyl
Cys	cysteine
d	doublet

DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCC	*N,N′*-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMEM	Dulbecco's modified eagle medium
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppe	ethylenebis(diphenylphosphine)
EGFR-TK	epidermal growth factor receptor tyrosine kinase
epi	epimers
equiv	equivalent(s)
Et	ethyl
EWG	electron-withdrawing group
FDA	Federal Drug Administration
gem	geminal

GI_{50}	50% growth inhibition concentration
h	hour(s)
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
HMDS	hexamethyldisilazane
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IP	intraperitoneal
K352A	lysine 352 to alanine
LAH	lithium aluminum hydride
LC	liquid chromatography
LDA	lithium diisopropylamide
lq	liquid
Lys	lysine
m	multiplet
m/z	mass:charge ratio
mAb	monoclonal antibody
Me	methyl
Mes	mesityl
min	minute(s)
mp	melting point
MS	mass spectrometry

NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIH	National Institutes of Health
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o	ortho
q	quartet
PBS	phosphate-buffered saline
PD	pharmacodynamic
PDB	protein data bank
PG	protecting group
Pgp	P-glycoprotein
Ph	phenyl
PK	pharmacokinetic
PMB	4-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTFE	polytetrafluoroethylene
^{i}Pr	isopropyl

pyr	pyridine
s	singlet
SAR	structure-activity relationship
SEM	standard error of measurement
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMT	trithiocyanuric acid
TOF	time-of-flight
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
U	units
UPLC	ultra performance liquid chromatography
UV	ultraviolet
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Xphos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

CHAPTER 1. MICROTUBULE-BINDING AGENTS AND OVARIAN CANCER

1.1 Introduction. For 2016, the National Institutes of Health estimates ovarian cancer will be the 5th leading cause of cancer-related deaths in women with 14,240 associated deaths.[1] The NIH also estimates 22,280 new diagnoses in 2016 and approximately 80% of ovarian cancer patients will relapse following treatment with first line taxane/platinum combination therapy.[1,2] Based on these statistics, novel ovarian cancer chemotherapeutic agents with new mechanisms of action are required. In 2011, Nikas and coworkers performed a bioinformatics study to identify genes overexpressed in short term ovarian cancer patients who survived < 3 years (short-term survivors) following platinum/taxol chemotherapy to patients who survived > 7 years (long-term survivors) after treatment.[3] One of the top predictive genes overexpressed in short-term survivors was *TUBA3C*, which encodes for α-tubulin. The overexpression of *TUBA3C* in short-term ovarian cancer survivors led us to believe α-tubulin would be a good target for new chemotherapeutic agents.

1.2 Microtubule-binding agents as chemotherapeutic agents. α-Tubulin and β-tubulin are structural proteins that polymerize to form microtubules. Microtubules play key roles in maintaining cell shape, organelle movement, and cell division.[4] During mitosis, microtubules are responsible for separating daughter chromatids during anaphase. Disruption of the polymerization dynamics between α-tubulin and β-tubulin to form microtubules during mitosis can result in cell cycle arrest at the G2/M phase and subsequent apoptosis. A number of FDA approved chemotherapeutic agent's mechanism of action involves the disruption of the polymerization dynamics by either stabilizing or

destabilizing microtubules;[5-7] these include the drugs derived from the taxanes, epothilones, and vinca alkaloid natural products as shown in Figure 1-1. More recently, analogs of the tubulin-binding natural products dolastatin 10 and maytansine have been utilized as the active small molecule in antibody-drug conjugates (Figure 1-2).[8,9]

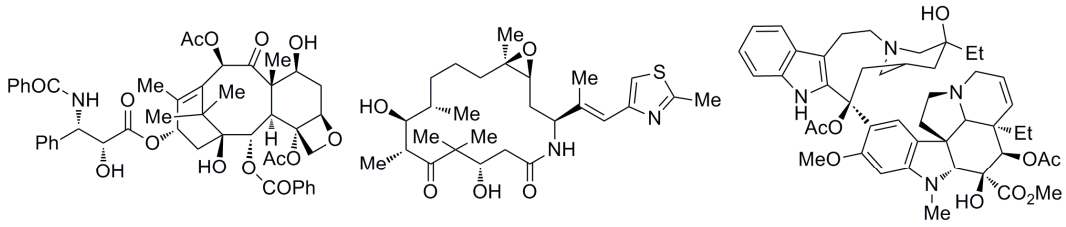


Figure 1-1. Examples of FDA-approved tubulin-binding chemotherapeutic agents.

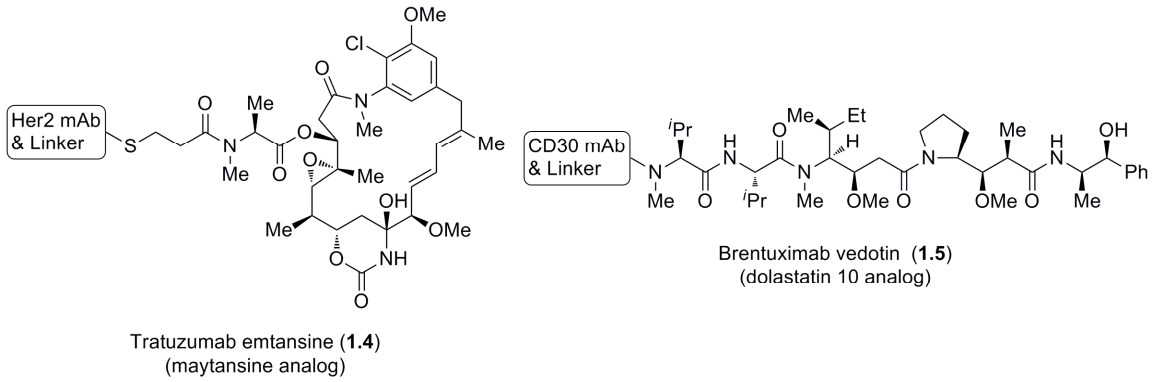


Figure 1-2. Structures of FDA-approved antibody-drug conjugates containing tubulin-binding chemotherapeutic agents

While these chemotherapeutic agents have diverse chemical structures, they have been shown to bind to β-tubulin via X-ray crystallography at different sites of the protein as shown in Figure 1-4.[10-14] While some compounds have overlapping binding sites, distinct binding sites have been identified; these include the taxane binding site, the vinca binding site, and the maytansine site.

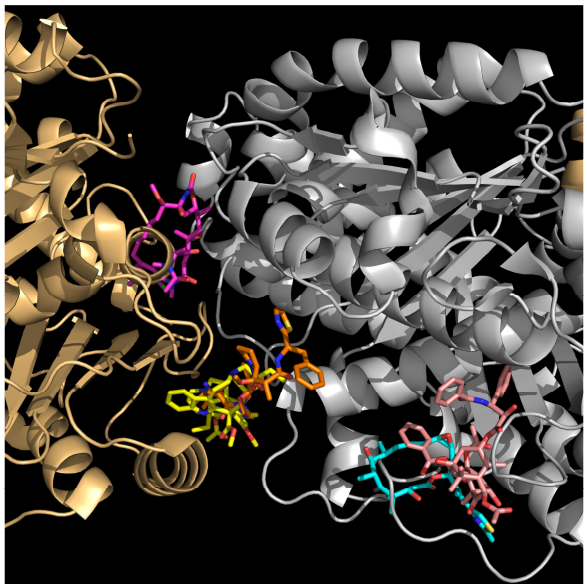
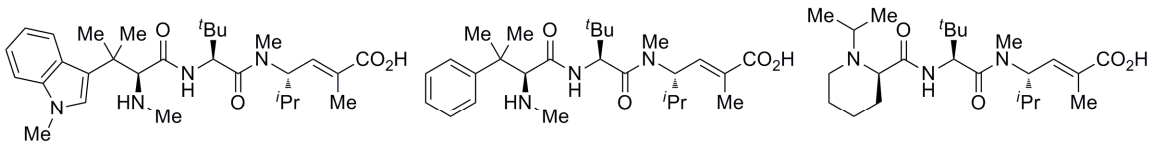


Figure 1-3. Overlay of X-ray crystal structures of tubulin-binding agents bound to β-tubulin. Protein (PDB ID 4X1I): α-tubulin (brown), β-tubulin (grey). Ligands: paclitaxel (pink, PDB ID 1JFF), epothilone A (cyan, PDB ID 4I50), vinblastine (yellow, PDB ID 1Z2B), maytansine (magenta, PDB ID 4TV8), dolastatin 10 analog PF-06380101 (orange, PDB ID 4X1I).

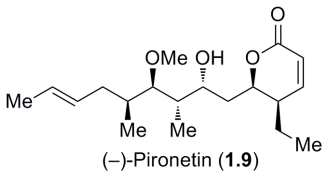
Although tubulin-binding chemotherapeutic agents have been successful for the treatment of a variety of cancers, drug-resistance has been reported for these agents.[7,15,16] In ovarian cancer patients, drug-resistance to paclitaxel has been associated with changes in the expression level of the different isoforms of β-tubulin; increased levels of class III β-tubulin was shown to correlate with shorter survival in ovarian cancer patients.[17,18] While a number of drugs have been developed that target β-tubulin, no current chemotherapeutic agents disrupt tubulin polymerization via binding to α-tubulin. A few natural products have been shown to bind to α-tubulin. One class of natural products shown to bind to α-tubulin is the hemiasterlins (Figure 1-4).[19-21] Hemiasterlin analogs Taltobulin/HTI-286 (**1.7**) and E7974 (**1.8**) have independently been developed as drug candidates and proceeded to Phase I clinical trials.[22,23] While the hemiasterlin analogs were shown to bind to α-tubulin via photo cross-linking studies, taltobulin (**1.7**) was shown to bind to the vinca binding site in β-tubulin via X-ray crystallography.[24]

Haematological toxicity was reported for analog **1.8**. In addition to the hemiasterlins, the natural product pironetin (Figure 1-4, **1.9**) has been shown to bind α-tubulin.



Hemiasterlin (**1.6**) Taltobulin/HTI-286 (**1.7**) E7974 (**1.8**)

Figure 1-4. Structure of hemiasterlin and related analogs.



(–)-Pironetin (**1.9**)

Figure 1-5. Structure of pironetin.

1.3 Background on pironetin. Pironetin is a polyketide natural product independently isolated from the fermentation of different *Streptomyces* strains in 1993 and 1994.[25-27]

1.3.1 Biological activity. While pironetin was initially reported as a plant growth inhibitor and immunosuppressant, it was subsequently shown to have potent *in vitro* antiproliferative activity with nanomolar GI_{50} values against a variety of cancer cell lines including ovarian cancer cells which overexpress the Pgp transporter.[28-32] The overexpression of Pgp transporters is another mechanism by which cancer cells can develop resistance to chemotherapeutic agents via efflux of chemotherapeutic agents out of the cell.[15] While pironetin has potent *in vitro* activity, it showed poor activity *in vivo* in mice bearing P388 murine leukemia cells.[33] A 6.25 mg/kg IP dose resulted in increased survival time from 11.2 days to 14.3 days. Animals treated with pironetin also showed severe weight loss.

1.3.2 Mechanism of action. In initial studies into pironetin's mechanism of action, the natural product was found to induce G2/M phase cell cycle arrest in 3Y1 normal rat

fibroblast cells.[33] This activity was similar to other chemotherapeutics which disrupt microtubule polymerization. In tubulin polymerization assays, pironetin has been reported in the literature to disrupt the polymerization dynamics by either stabilizing[31] or destabilizing[34] microtubules. To further study pironetin's mechanism of action, groups have identified the pironetin binding site. In 2004, Usui and coworkers incubated pironetin with α- and β-tubulin and found that pironetin labeled a 100 amino acid sequence of α-tubulin.[35] Lysine 352 was identified as the residue involved in the binding with α-tubulin after alanine scanning of nucleophilic residues in this 100 amino acid sequence; the K352A mutation in α-tubulin resulted in an 80% decrease in pironetin binding. The group proposed pironetin's mechanism of action involved formation of a covalent adduct via conjugate addition of lysine 352 of α-tubulin as shown in Figure 1-6.

In 2016, the X-ray crystal structures of pironetin bound to α-tubulin was independently reported by two groups.[36,37] In these crystal structures, the natural product binds in an unique pocket not observed in the apo structure as shown in Figure 1-7. Pironetin formed a covalent adduct with cysteine 316 instead of lysine 352. The covalent adduct formed between pironetin and α-tubulin was also detected by MS/MS spectrometry following incubation of pironetin with α- and β-tubulin. The previous observation of the K352A mutation in α-tubulin resulting in loss of pironetin binding could be due to lysine 352 being involved in the binding by deprotonating cysteine 316 or having a role in stabilizing pironetin's unique binding pocket.

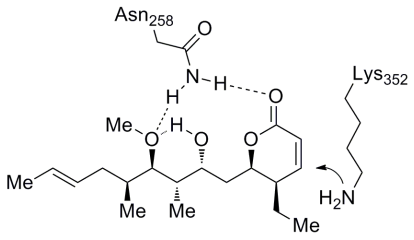


Figure 1-6. Usui and coworkers' proposed binding model of pironetin to α-tubulin.

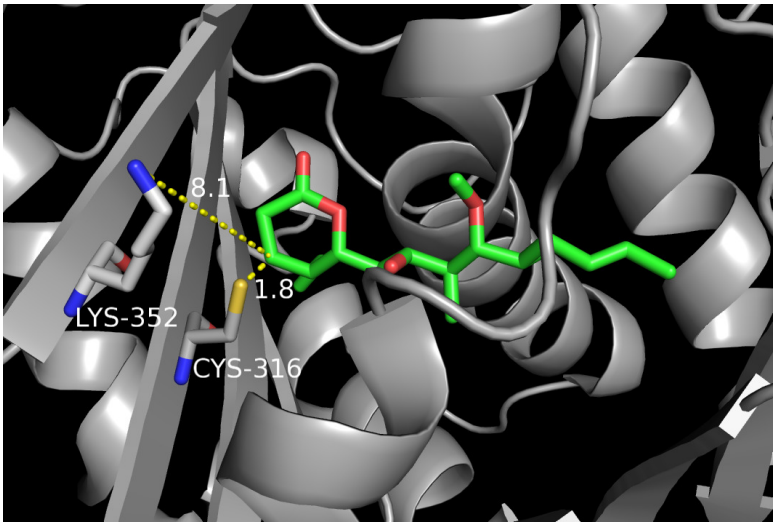


Figure 1-7. Bond distances between pironetin and residues Lys_{352} and Cys_{316} of α-tubulin (PDB ID 5FNV).

1.4 Summary. Pironetin is a natural product that has potent antiproliferative activity and a novel mechanism of action via its binding to α-tubulin. These properties make it a potential candidate for development as a chemotherapeutic agent.

CHAPTER 2. EVALUATION OF PIRONETIN'S BIOLOGICAL ACTIVTY AND PHARMACOLOGIAL PROPERTIES.

2.1 Introduction. While pironetin (**2.1**) is reported to have potent antiproliferative activity *in vitro* against various cancer cell lines, the natural product has not been further developed as a drug candidate. The initial goal of our research was to evaluate whether the natural product would be a good candidate to develop into an ovarian cancer chemotherapeutic agent. Thus we sought to confirm pironetin's previously reported biological activity and evaluate its pharmacokinetic and pharmacodynamic properties, which had not been previously reported in the literature.

2.2 Isolation of pironetin. Since significant amounts of pironetin could potentially be required for development of the natural product into a drug, we sought to obtain pironetin from a biological source instead of through commercial vendors. Our group obtained the previously reported pironetin-producing *Streptomyces prunicolor* strain PA-48153.[25] The culture was given to the University of Minnesota Institute for BioTechnology for fermentation in a 200 L reactor. The fermentation resulted in 165 kg of fermentation broth and also 40 kg of cell paste. Pironetin was isolated from both the fermentation broth and cell paste. While the extraction of pironetin from the cell paste was adapted from previously reported procedures, we performed the extraction from the fermentation broth through an alternative procedure.[25] In the previously published procedure for the extraction of pironetin, the fermentation broth was extracted with ethyl acetate in a 2:1 ratio of fermentation broth to ethyl acetate. Due to the large volume of fermentation broth generated in our 200 L fermentation, large volumes of ethyl acetate and specialized

equipment would be required for the extraction following this procedure. To facilitate the extraction of pironetin from our large volume of fermentation broth, we performed the extraction from the fermentation broth with a solid-phase resin that absorbs organic compounds from aqueous mixtures. After incubating overnight in the fermentation broth, the resin was recovered following filtration of the resulting suspension. The resin was rinsed with methanol to release absorbed organic compounds. Crude extracts from both the cell paste and the fermentation both could be purified via standard normal-phase and reverse-phase chromatography to obtain pironetin in ≥95% purity.

2.3 Evaluation of pironetin's antiproliferative activity. The initial step in evaluating pironetin as a drug candidate was to confirm its previously reported antiproliferative activity. We obtained drug-sensitive OVCAR5 ovarian cancer cell lines along with a cisplatin-resistant A2780-CP ovarian cancer cell line and its drug-sensitive parent A2780 cell line. The antiproliferative activity of pironetin in these cell lines was evaluated along with the ovarian cancer chemotherapeutic agents cisplatin and paclitaxel. In addition to paclitaxel, we also compared pironetin's biological activity to the tubulin-binding agents vinblastine and Taltobulin/HTI-286. Taltobulin/HTI-286 is a hemiasterlin analog and Phase I clinical candidate previously shown to bind to α-tubulin binding. The measured GI_{50} values for each compound are reported in Table 2-1.

Table 2-1. Antiproliferative activity of pironetitn and others drugs and clinical candidates

		GI_{50} (nM)[a]		
Entry	Compound	OVCAR5[b]	A2780[b]	A2780-CP[c]
1	Pironetin (**2.1**)	40.5 ± 6.9	35.7 ± 1.5	25.0 ± 1.2
2	Cisplatin	32,700 ± 10,100	1,680 ± 330	21,500 ± 900
3	Paclitaxel	84.2 ± 16.7	5.52 ± 0.75	13.8 ± 0.8
4	Vinblastine	0.134 ± 0.034	0.507 ± 0.067	3.48 ± 0.25
5	Taltobulin/HTI-286	0.0379 ± 0.0026	0.535 ± 0.036	0.556 ± 0.008[d]

[a] Average of 2 experiments performed in triplicate ± SEM (n = 6)
[b] Drug-sensitive ovarian cancer cell line
[c] Cisplatin-resistant ovarian cancer cell line
[d] Average of 2 experiments performed in triplicate and duplicate ± SEM (n = 5)

Pironetin (Table 2-1, entry 1) was found to have nanomolar GI_{50} values against the various cell lines with comparable activity to paclitaxel (Table 2-1, entry 3). Our measured GI_{50} value in the A2780 cell line was higher than the previously reported value of 2.9 nM for this cell line.[28] Although pironetin was less active than other tubulin binding agents vinblastine (Table 2-1, entry 4) and Taltobulin (Table 2-1, entry 5), we believed the natural product had sufficient *in vitro* potency to warrant further evaluation as a drug candidate.

2.4 Evaluation of pironetin's pharmacokinetic and pharmacodynamic properties. After confirming pironetin's *in vitro* antiproliferative activity, we were interested in evaluating its efficacy *in vivo*. In a previously reported *in vivo* study, pironetin had poor efficacy in mice bearing murine P388 leukemia.[33] Significant weight loss was also observed in mice dosed with pironetin. Pironetin's poor *in vivo* efficacy could be due to the natural product having poor ADME properties such as poor bioavailability, poor stability, poor distribution, and/or rapid clearance. To evaluate if these properties were a cause for pironetin's poor *in vivo* efficacy, we chose to evaluate the natural product's PK/PD properties prior to performing *in vivo* efficacy studies.

2.4.1 Evaluation of pironetin's solubility and protein binding. One potential cause of pironetin's poor *in vivo* efficacy could be the natural product's poor solubility in biological media. If pironetin had poor solubility, the natural product could precipitate following administration and result in the poor drug adsorption and *in vivo* efficacy. To evaluate its solubility, pironetin was sent CEREP, a CRO, for solubility assays in pH = 7.4 PBS, simulated intestinal fluid and simulated gastric fluid. The solubility of pironetin was evaluated at 200 μM in these different solutions. In the simulated intestinal fluid and simulated gastric fluid, pironetin was found to have solubility of 141.3 μM and 198.4 μM respectively. For the pH = 7.4 PBS, pironetin soluble at the highest measured concentration of 200 μM. Based on the high solubility of pironetin in the various fluids, we did not believe the natural product's solubility was a significant factor in pironetin's poor *in vivo* efficacy.

Another factor which could impact pironetin's *in vivo* efficacy could be its drug distribution following dosing. One factor which could impact distribution is protein binding; if pironetin is predominately bound to plasma proteins in animals, the natural product would not be circulating at sufficient concentrations to inhibit tumor growth. We contracted CEREP to evaluate protein's protein binding in plasma in human, mouse and rat plasma. We chose to evaluate the property in both mouse and rat plasma in addition to human plasma since future *in vivo* studies could be performed in either rats or mice. The calculated percent of protein-bound of pironetin ranged from 87% in human plasma to 98% in mouse plasma; the calculated percent of pironetin bound to proteins in rat plasma was 93%. While we initially hypothesized the high percent protein binding in

mouse plasma could be the cause of pironetin's poor *in vivo* efficacy in mice, a survey in 2014 reported compounds with high protein binding have been approved as drugs by the FDA. The survey reported 45% of newly approved drugs have >95% protein binding while 24% of new drugs have >99% protein binding.[38] Based on this survey, we did not believe pironetin's high protein binding was a significant factor for the poor *in vivo* efficacy and thus decided to explore additional pharmacokinetic properties of pironetin.

2.4.2 Evaluation of pironetin's stability. Another potential cause for pironetin's poor *in vivo* efficacy could be the natural product's stability when dosed in animals. Pironetin could potentially decompose in biological fluids and/or be metabolized by the liver. Although stability assays could be performed *in vivo*, we chose to evaluate this property *in vitro* since *in vitro* assays would provide preliminary data and require smaller quantities of material relative to *in vivo* assays.

2.4.2.1 Synthesis of a model system. For our studies on the stability of pironetin, we required a reference standard for quantitative measurements during our assays. Since many analytical analysis methods for assays are performed on a HPLC instrument equipped with a UV detector, we chose to synthesize a standard with similar UV absorbance as pironetin. We chose to synthesize reference **2.2** (Figure 2-1), which contains both an *E*-non-conjugated olefin along with an α,β-lactone similar to pironetin. We proposed the lactone in standard **2.2** could be synthesized following lactonization of *Z*-olefin **2.3**, as shown in Scheme 2-1. Intermediate **2.3** could be synthesized via a Z-selective olefination reaction of aldehyde **2.4**, which could be derived from methyl acetoacetate (**2.5**).

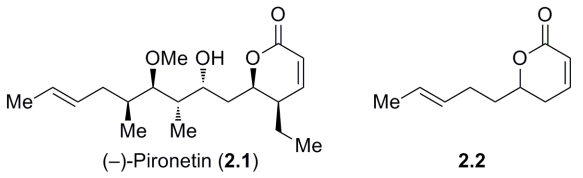
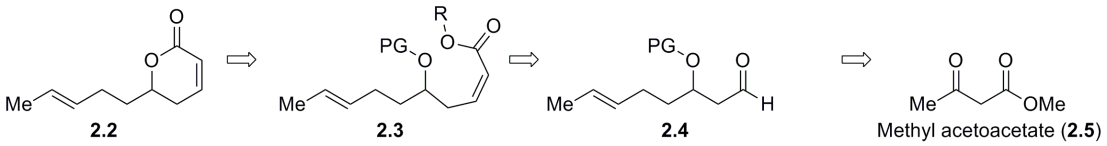


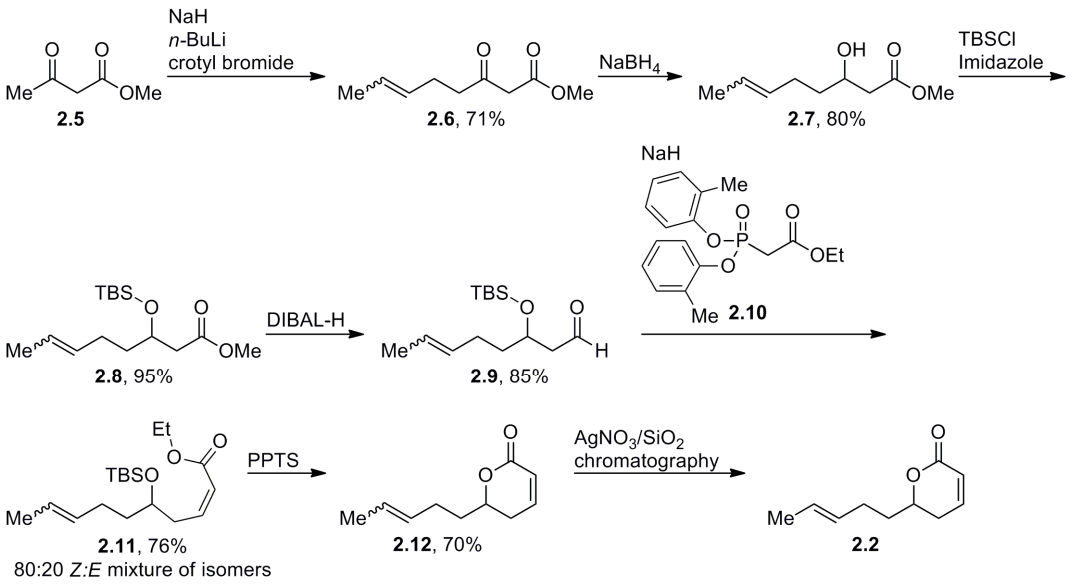
Figure 2-1. Structure of pironetin and proposed internal standard.

Scheme 2-1. Retrosynthesis of internal standard **2.2**



The forward synthesis of standard **2.2** began with the alkylation of the dianion of methyl acetoacetate (**2.5**) with a predominately *trans*- mixture of crotyl bromide as shown in Scheme 2-2. β-Keto-ester **2.6** was reduced to secondary alcohol **2.7**, and subsequently protected as the TBS ether. The methyl ester in intermediate **2.8** was reduced to the aldehyde **2.9**. Olefination of aldehyde **2.9** with phosphonate ester **2.10** resulted in the Z-olefin. Ando and coworkers previously reported the olefination of β-silyloxy aldehydes with phosphonate ester containing aromatic groups such as **2.10** to proceed in >90% yield with 95:5 selective for the *Z*-olefin over the *E*-olefin.[39] Treatment of intermediate **2.11** with PPTS resulted in a one-pot deprotection of the silyl ether and lactonization to form standard **2.12** as a mixture of diastereomers. The two diastereomers could be separated via silver-nitrate embedded silica gel column chromatography to yield the desired standard **2.2**.

Scheme 2-2. Synthesis of standard **2.2**



2.4.2.2 Evaluation of pironetin's serum stability. To evaluate pironetin's stability in biological systems, we first chose to evaluate the natural product's serum stability. Similar to the protein binding assays, the serum stability was evaluated in human, mouse and rat sera. Pironetin was incubated in the sera of the different species at 37 °C. The amount of pironetin remaining in serum was calculated by quenching aliquots of serum with a solution of standard **2.2**. The percentage of pironetin remaining in serum at multiple time points over a 24 h incubation are shown in Table 2-2.

Table 2-2. Serum stability of pironetin

	Percent Pironetin Remaining in Serum (%)[a]		
Time	Human	Rat	Mouse
10 min	90.0 ± 4.3	90.9 ± 5.1	107 ± 5
30 min	80.0 ± 5.8	94.4 ± 1.9	103 ± 10
1 h	83.0 ± 5.1	87.3 ± 2.1	102 ± 6
2 h	83.1 ± 6.4	78.0 ± 2.8	97.8 ± 2.7
4 h	74.4 ± 3.3	69.8 ± 2.1	89.8 ± 0.2
8 h	67.5 ± 2.2	51.5 ± 3.2	79.5 ± 5.3
24 h	50.0 ± 1.3	35.4 ± 3.6	56.5 ± 5.9

[a]Tested at ~2.4 mM at 37 °C with 0.1% DMSO. Average of 3 runs ± SEM.

Pironetin was found to have moderate serum stability with 35-57% of the natural product remaining after incubation at 37 °C for 24 h. Since pironetin was found to be stable in biological media, we continued to evaluate additional pharmacological properties of pironetin.

2.3.2.3 Evaluation of pironetin's metabolic stability. Another potential cause for pironetin's poor *in vivo* efficacy could be the rapid metabolism of the natural product to an inactive metabolite. Preliminary *in vitro* metabolic stability assays were performed in human, mouse, and rat liver microsomes by CEREP. Liver microsomes consist of fractions derived from the liver containing metabolic enzymes and mimic the *in vivo* metabolism by the liver. In human liver microsomes, the half-life of pironetin was calculated to be 7 min; the half-lives were not calculated in mouse or rat liver microsomes due to complete metabolism of the natural product within 15 min. Due to these short half-lives, we hypothesize the poor metabolic stability of pironetin was the primary cause of the poor activity in the previous *in vivo* study in mice.

2.3.3 Evaluation of non-selective covalent adduct formation with pironetin. Along with evaluating the PK properties of pironetin which could impact the natural product's efficacy, we also sought to determine potential causes of pironetin's *in vivo* toxicity. Since pironetin is a covalent inhibitor, we hypothesized the toxicity could be due to the natural product forming covalent adducts in a non-selective manner with other proteins. To evaluate if pironetin could form covalent adducts with other biomolecules, we monitored covalent adduct formation between pironetin and the monoethyl ester of glutathione, which contains a reactive thiol. Following incubation of pironetin with an

excess of glutathione monoethyl ester in pH 7 PBS at 37 °C, a 1:1 mixture of pironetin to glutathione-pironetin adduct was detected by LC-MS/MS. Since pironetin formed adducts with glutathione, we hypothesized it could also form adducts with additional proteins containing a reactive cystine residue. This off-target binding could be the cause of the severe weight loss in animals dosed with the natural product.

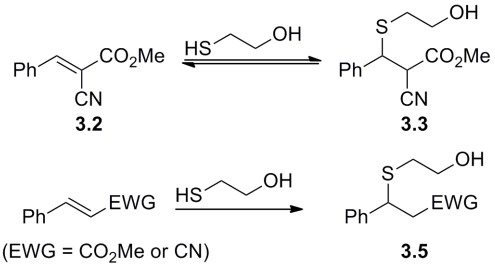
2.5 Conclusion. Following isolation of pironetin from a fermentation of *Streptomyces prunicolor* strain PA-48153, we confirmed its previously reported antiproliferative activity. Pironetin was found to have nanomolar GI_{50} values against a panel of ovarian cancer cell lines with comparable antiproliferative activity as paclitaxel. To determine if pironetin would be a good drug candidate, we evaluated multiple PK/PD properties of the natural product. Pironetin was found to be rapidly metabolized in human liver microsomes and to form covalent adducts with reactive thiols. These poor PK/PD properties could be the cause for the previously observed poor *in vivo* efficacy in mice bearing P388 murine leukemia cells. Due to its poor PK/PD properties, we chose not to pursue developing pironetin as a single agent drug candidate. However, we believed pironetin's PK/PD properties could be improved via modification at different positions of pironetin. Pironetin analogs with potent antiproliferative activity and with improved PK/PD properties could provide a potential candidate for development into a chemotherapeutic agent.

CHAPTER 3. SYNTHESIS AND EVALUATION OF α-FUNCTIONALIZED PIRONETIN ANALOGS

3.1 Introduction. In our studies into the PK/PD properties of pironetin (**3.1**), we found the natural product could form covalent adducts with proteins and other biological molecules containing a reactive thiol. We hypothesized that the non-selective covalent adduct formation could be the cause of the previously observed *in vivo* toxicity. To decrease its toxicity, we sought to synthesize pironetin analogs with decreased off-target covalent adduct formation.

In previous reports on improving the drug properties of Michael acceptors, researchers reported that the addition of functional groups at the α-position of Michael acceptors can decrease covalent-adduct formation. Taunton and coworkers initially reported α-nitrile containing Michael acceptor **3.2** formed reversible covalent adducts with thiols, whereas non-substituted Michael acceptor **3.4** formed irreversible adducts (Scheme 3-1).[40]

Scheme 3-1. Reversible conjugate addition to α-functionalized Michael acceptors



3.2 **3.3**

3.4 (EWG = CO_2Me or CN) **3.5**

Taunton and coworkers proposed the Michael addition of the nitrile at the α-position of Michael acceptor **3.2** is reversible since the increased acidity of the α-hydrogen in adduct **3.3** can undergo deprotonation allowing for a more rapid elimination of the thiol to regenerate the conjugated ester. Taunton and coworkers subsequently found Michael

acceptors containing electron-deficient aromatic groups including heterocycles at the α-position also form reversible covalent bonds with thiols.[41] A reversible covalent inhibitor would have decreased off-target binding compared to the irreversible inhibitor. In a separate study into modifying the electronic properties of Michael acceptors, Yu and coworkers evaluated the effect of adding a fluorine to the EGFR-TK covalent inhibitor afatinib (**3.6**) (Figure 3-1);[42] the group found that the fluorine-containing analog **3.7** had significantly decreased covalent adduct formation when incubated with glutathione over the parent drug. Based on these previous studies, we sought to synthesize pironetin analogs containing different functional groups at the α-position of the α,β-unsaturated lactone to decrease off-target binding. SAR studies at the α-position of pironetin have not been previously reported in the literature.

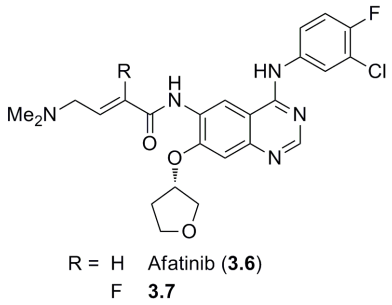
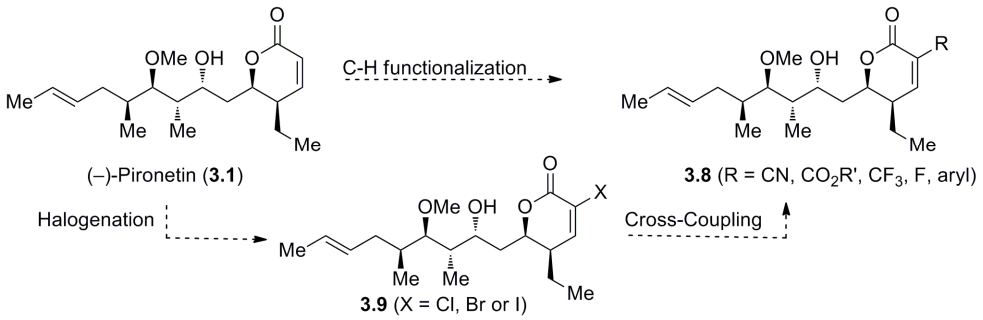


Figure 3-1. Structure of afatinib and related α-functionalized analog.

3.2 Potential synthetic routes to α-functionalized pironetin analogs via semi-synthesis. Due to the complexity of the natural product's structure, the most rapid method to synthesize α-functionalized pironetin analogs **3.8** would be via semi-synthesis from pironetin isolated from our previous fermentation. We hypothesized two potential routes for the semi-synthesis of desired analogs as shown in Scheme 3-2.

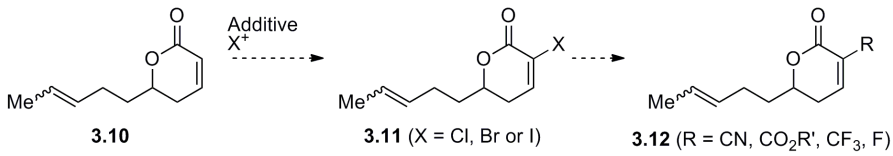
Scheme 3-2. Potential synthetic routes to α-functionalized pironetin analogs via semi-synthesis



One potential route involves installation of desired functional group at the α-position via a direct C-H activation at the α-position. An alternative synthetic route for analogs **3.8** involved initial halogenation of the α-position resulting in intermediate **3.9.** The desired functional groups at the α-position could subsequently be introduced via a cross-coupling reaction. Although the direct C-H functionalization route would be the most efficient route to install a functional group at the α-position, methods for the direct C-H functionalization are not well developed for complex natural products. Thus, we sought to explore synthesis of analog **3.8** via the later 2-step halogenation/cross-coupling synthetic route.

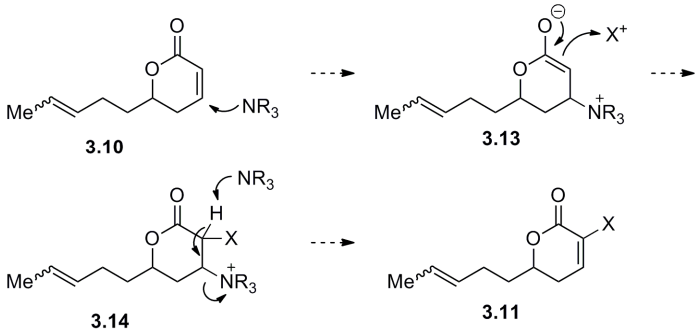
To explore the feasibility of synthesizing pironetin analogs **3.8** via a halogenation/cross-coupling route, we screened potential reaction conditions using model substrate **3.10**, which contains both a non-conjugated olefin and α,β-unsaturated lactone similar to pironetin (Scheme 3-3).

Scheme 3-3. Potential synthetic routes for the α-functionalization of substrate **3.10**



The initial challenge in this synthetic route was the selective halogenation of the conjugated-olefin over the non-conjugated olefin. We hypothesized that the α,β-unsaturated lactone could be selectively-activated for halogenation by a tertiary amine similar to the activation of α,β-unsaturated carbonyl compounds in Bayliss-Hillman reactions. A potential mechanism for the activation of the conjugated olefin is shown in Scheme 3-4. We hypothesized the tertiary amine would activate the conjugated olefin via hetera-Michael addition into substrate **3.10**; the resulting enolate **3.13** could be halogenated by an electrophilic halogen source. Elimination of the amine adduct from intermediate **3.14** would result in the desired halogenated substrate **3.11**.

Scheme 3-4. Potential mechanism for the halogenation of substrate **3.10**



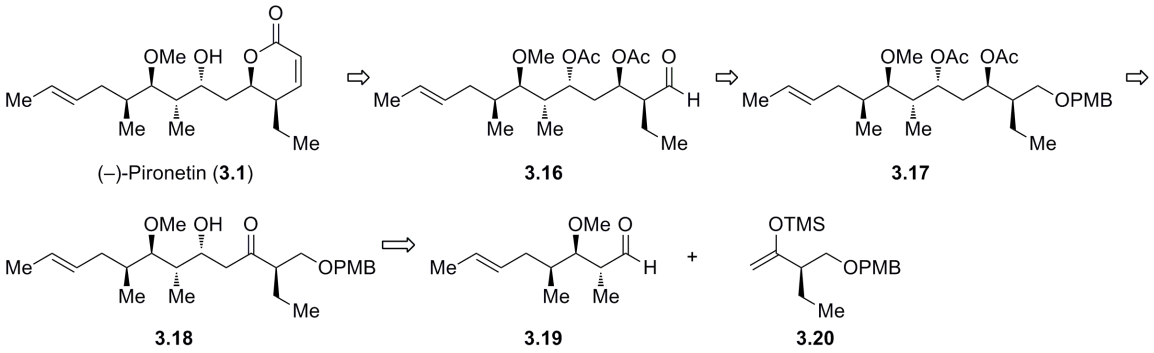
We explored the halogenation of substrate **3.10** with electrophilic halogenation reagents Br_2, I_2, NBS, or NIS in the presence of tertiary amine additives DABCO, TEA or DMAP. These reactions resulted in a complex mixture of products resulting from the non-selective halogenation of either olefin along with unreacted starting material. Due to the lack of selectively for the halogenation of the model substrate **3.10** and the limited quantities of pironetin we had obtained from our fermentation, we chose to synthesize α-functionalized pironetin analogs **3.8** via total synthesis instead of semi-synthesis.

3.3 Synthesis towards α-cyanopironetin via total synthesis. Because Taunton's initial reports on reversible covalent inhibitors involved α-nitrile containing Michael acceptors, the first α-functionalized pironetin analog we sought to synthesize via total synthesis was α-cyanopironetin **3.15**.

3.3.1 First generation route. Since a number total syntheses of pironetin have been reported in the literature,[43-55] we chose to adapt previously reported syntheses for the synthesis of α-cyanopironetin **3.15**.

3.3.1.1. Keck's pironetin total synthesis. After surveying the different total syntheses of pironetin, we chose to adapt synthetic strategies previously utilized by Keck and coworkers for the total synthesis of pironetin (Scheme 3-5).[50] In Keck's total synthesis of pironetin, the α,β-unsaturated lactone was synthesized via lactonization methodology of β-acetoxy aldehydes developed in his group.[56] Aldehyde **3.16** was synthesized from intermediate **3.18** via a series of functional group transformations. β-Hydroxy ketone **3.18** was synthesized via a stereoselective Mukaiyama aldol reaction between aldehyde **3.19** and silyl enol ether **3.20**.

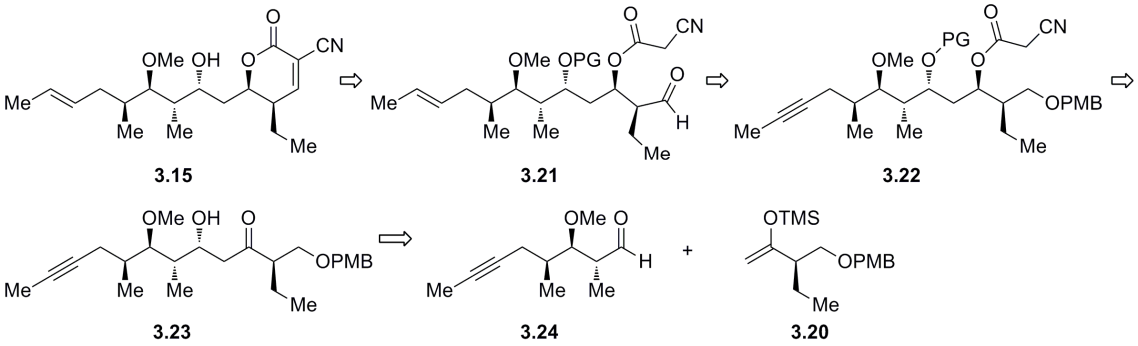
Scheme 3-5. Retrosynthesis from Keck's pironetin total synthesis



3.3.1.2. Retrosynthesis. We believed that the Keck total synthesis would be amenable for the synthesis of analog **3.15** since we proposed to synthesize the α-cyano-α,β-

unsaturated lactone via an intramolecular Knoevenagel condensation between the cyanoacetate and aldehyde in intermediate **3.21** as shown in Scheme 3-6. Intermediate **3.21** is similar to aldehyde **3.16** from Keck's total synthesis with the main difference being the cyanoacetate group in intermediate **3.21** compared to the acetate group in Keck's intermediate **3.16**. Aldehyde **3.21** would be derived from alkyne **3.22**. Intermediate **3.22** differs from Keck's intermediate **3.17** in that the former contains an alkyne instead of a *trans*-olefin. In our proposed route, we planned to install the *trans*-olefin from the alkyne during the late stages of the synthesis. The alkyne could be converted to the trans-olefin under dissolving metal reduction conditions that also remove the PMB protecting group in intermediate **3.22**. A similar transformation was previously utilized by the Dias group in their total synthesis of pironetin.[46] Intermediate **3.22** would be derived from the β-hydroxy ketone **3.23**, which would result from a Mukaiyama aldol between alkyne containing aldehyde **3.24** and the previously reported silyl enol ether **3.20** form Keck's total synthesis.

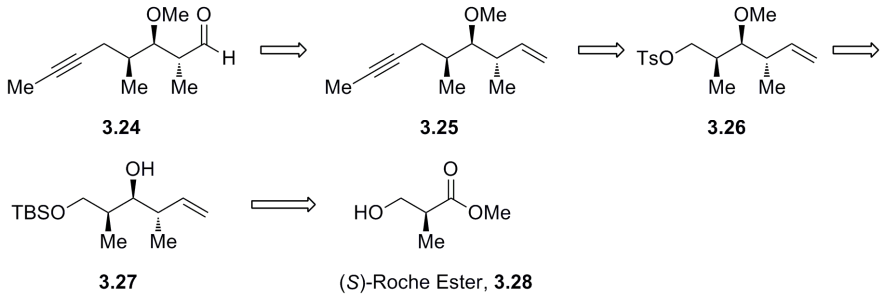
Scheme 3-6. Retrosynthesis for α-cyanopironeitn **3.15**



For the synthesis of aldehyde **3.24**, we proposed that the aldehyde could be synthesized from primary olefin intermediate **3.25** as shown in Scheme 3-7. The alkyne could be introduced via a displacement of the primary tosylate in intermediate **3.26**. Similar

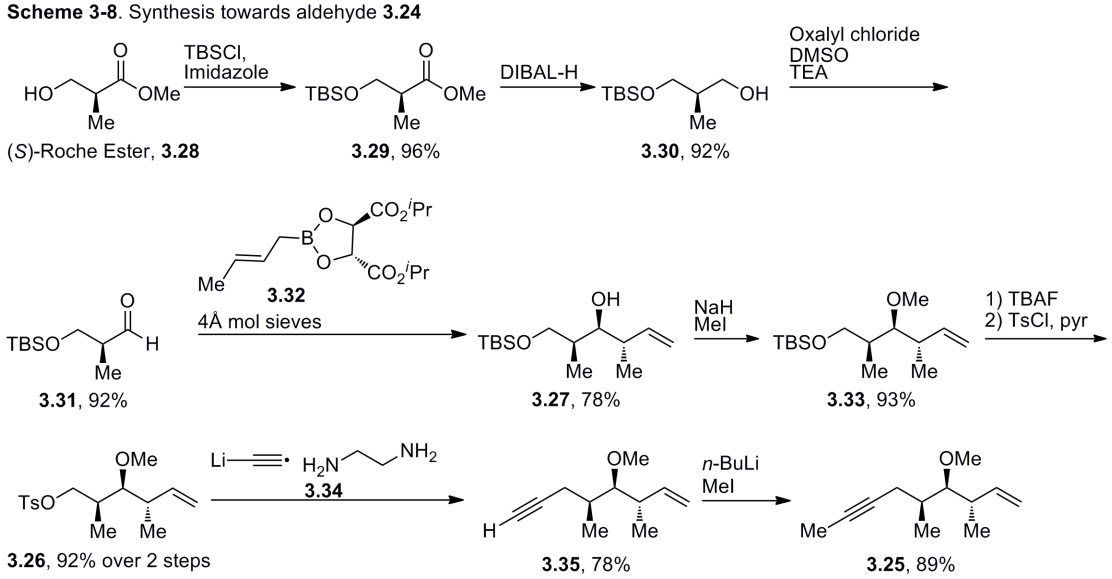
strategies for introduction of an alkyne have been utilized in previous total syntheses of pironetin.[43,46,54] Tosylate **3.26** would be synthesized from previously reported secondary alcohol **3.27** which can be derived from commercially available (*S*)-Roche ester (**3.28**).

Scheme 3-7. Retrosynthesis of fragment **3.24**



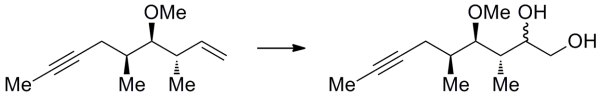
3.1.1.3 Forward Synthesis. Our forward synthesis began with the protection of the primary alcohol of (*S*)-Roche ester (**3.28**) as the TBS ether followed by a 2-step conversion of the methyl ester to the aldehyde as shown in Scheme 3-8. Aldehyde **3.31** was reacted with the Roush organoboron crotylation reagent **3.32**[57,58] to give the desired secondary alcohol **3.27** in good yield. Alkylation of the secondary alcohol with iodomethane and conversion of the TBS ether to the primary tosylate resulted in the desired intermediate **3.26** in 86% yield over 3 steps. The alkyne was installed via displacement of the tosylate with commercially available lithium acetylide complex **3.34**. The terminal alkyne was alkylated with iodomethane after reaction with *n*-BuLi to give intermediate **3.25**.

Scheme 3-8. Synthesis towards aldehyde **3.24**



We initially attempted to convert intermediate **3.25** directly to the desired aldehyde **3.24** via ozonoylsis, but only obtained the desired product in 16% yield even when the reaction was performed in the presence of an ozonizable dye.[59] An alternative strategy to convert the terminal olefin to the aldehyde, we proposed to perform the dihydoxylation of intermediate **3.25** followed by oxidative cleavage of the resulting diol **3.36** to the desired aldehyde. We screened various conditions for both the dihydroxylation and oxidative cleavage as shown in Table 3-1 and Table 3-2 respectively.

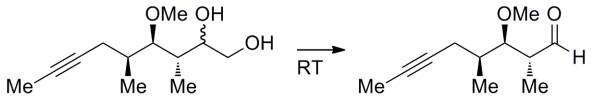
Table 3-1. Screen of dihydroxylation conditions of intermediate **3.25**



3.25 **3.36**

Entry	Reaction Conditions	Yield
1	5% OsO_4, 2 equiv NMO ^{t}BuOH, THF:H_2O (5:5:1), RT	64%
2	5% OsO_4, 2.4 equiv NMO Acetone:H_2O (1:2), RT	45%
3	AD-mix-α (0.2% [Os] × 2) ^{t}BuOH:H_2O (1.1:1), 0 °C	78%

Table 3-2. Screen of oxidative cleavage conditions of diol **3.36**

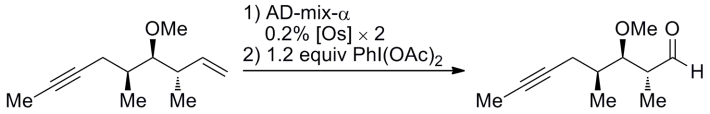


3.36 **3.24**

Entry	Reaction Conditions	Yield
1	3 equiv $NaIO_4$ THF:pH 7 buffer (4:1)	60%
2	1.2 equiv $PhI(OAc)_2$ DCM	67%
3	1.8 equiv $Pb(OAc)_4$ DCM	48%

We found the optimal reactions conditions for the conversion of intermediate **3.25** to aldehyde **3.24** to be via dihydroxylation with AD-mix-α[60] (Table 3-1, entry 3) followed by oxidative cleavage with (diacetoxyiodo)benzene[61] (Table 3-2, entry 2). The reaction sequence could be performed without purification of the intermediate diol **3.36** to give the desired product in 60% yield over 2 steps (Scheme 3-9). Although the stereochemistry of secondary alcohol intermediate diol **3.36** is insignificant in the dihydroxylation/oxidative cleavage sequence, we were interested if different AD-mix mixtures would impact the dihydroxylation and oxidative cleavage of olefin **3.25**. The same reactions in Scheme 3-9 performed with AD-mix-β instead of AD-mix-α resulted in the synthesis of aldehyde **3.24** in decreased yield of 40%; these results suggest potential substrate preference for the dihydroxylation of olefin **3.25** with the AD-mix-α.

Scheme 3-9. Two-step dihydroxylation/oxidative cleavage of intermediate **3.25**

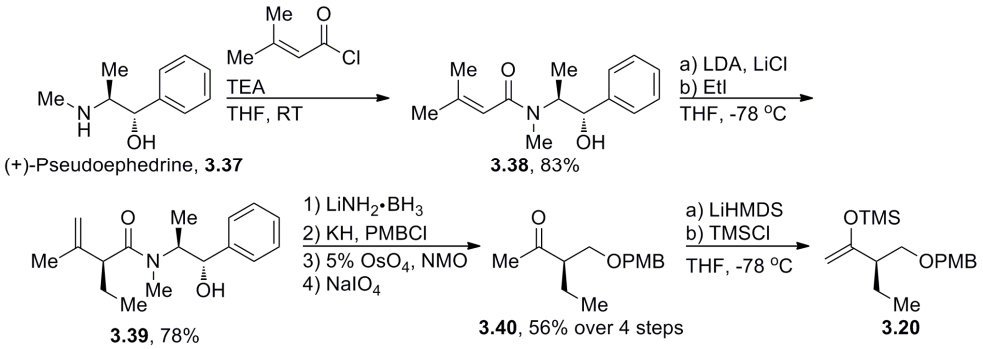


3.25 **3.24**, 60% over 2 steps

Following completion of the synthesis of the aldehyde **3.24**, the desired Mukaiyama aldol silyl enol **3.20** was synthesized following minor modification of Keck's

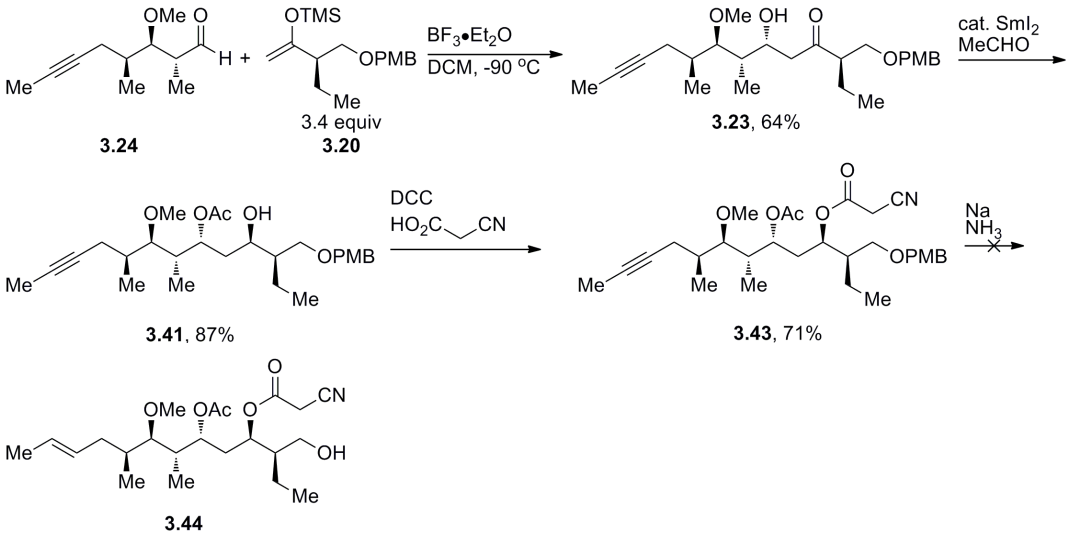
reported route as shown in Scheme 3-10.[50] The synthesis of the silyl enol ether began with the diastereoselective alkylation of the dienolate of amide **3.38** to give olefin **3.39**. Pseudoephedrine amide **3.39** was reduced to the primary alcohol and protected as the PMB ether. Methyl ketone **3.40** was synthesized following by dihydoxylation/oxidative cleavage of the 1,1-disubsituted olefin. Our synthesis of ketone **3.40** varied from Keck's synthesis in that we performed the PMB ether synthesis with commercially available PMBCl instead of PMBBr. Following Keck's previously reported reaction conditions, silyl enol ether **3.20** was synthesized via trapping of the lithium enolate of ketone **3.40** with TMSCl. The crude silyl enol ether was used without further purification.

Scheme 3-10. Synthesis of silyl enol ether **3.20**



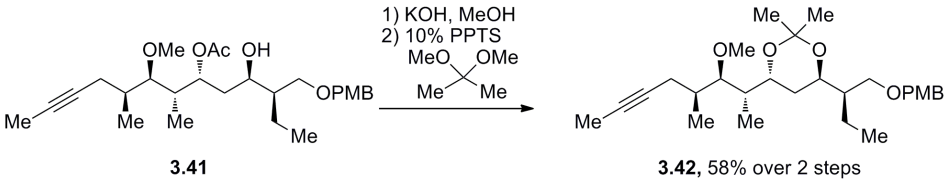
Crude silyl enol ether **3.20** was reacted with aldehyde **3.24** in the presence of BF_3•Et_2O to give the desired β-hydroxy ketone **3.23** in good yield (Scheme 3-11). Evans and coworkers developed models for the Mukaiyama aldol between silyl enol ethers and aldehydes containing either an α-substituent and/or a β-alkoxy substituent.[62] The model predicts the addition of silyl enol ether **3.20** would be directed to the desired *Re* face of aldehyde **3.24** in the presence of BF_3•Et_2O by both the α-and β-stereocenters to give desired product **3.23**.

Scheme 3-11. Progress on the first generation route to α-cyanopironeitn **3.15**



A samarium-catalyzed Evans-Tischenko[63] disproportionation reaction between β-hydroxy ketone **3.23** and acetaldehyde resulted in the simultaneous protection of the secondary alcohol as the acetate ester and directed reduction of the ketone. Enders and coworkers previously used a similar reaction in their total synthesis of pironetin.[47] To confirm the relative configuration from the disproportionation reaction, intermediate **3.41** was converted to acetonide **3.42** over 2 steps as shown in Scheme 3-12. The ^{13}C NMR resonances of for the acetonide (Figure 3-2) were consistent with chemical shifts reported by Rychnovsky and coworkers for the corresponding *anti*-1,3-diol acetonide.[64]

Scheme 3-12. Synthesis of acetonide **3.42** for ^{13}C NMR analysis



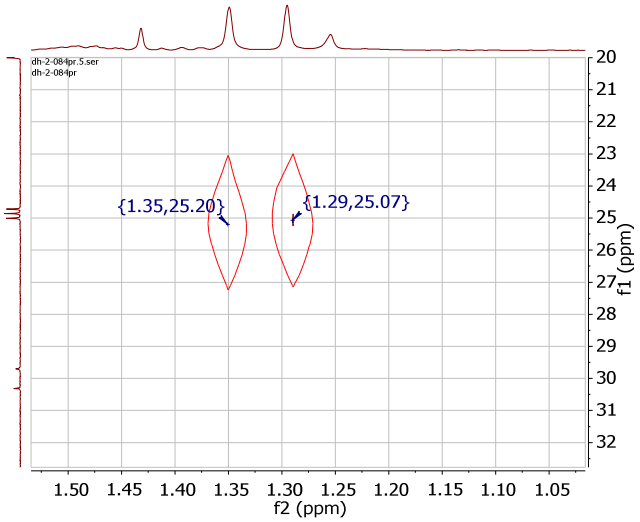


Figure 3-2. HMQC crosspeaks of acetonide **3.42**.

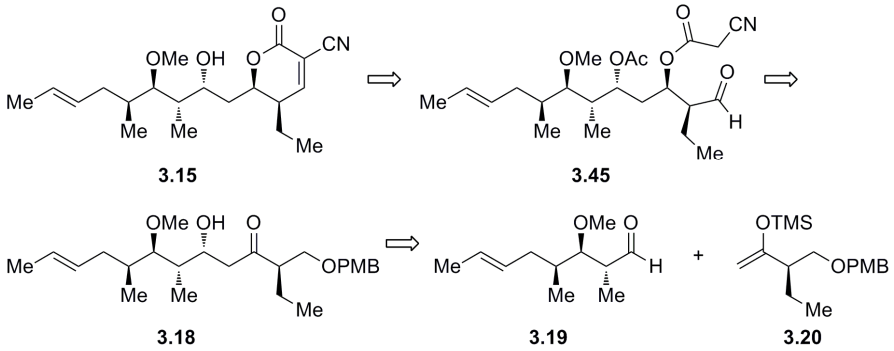
The synthesis towards α-cyanopironetin analog **3.15** continued with the DCC coupling of the secondary alcohol **3.41** with cyanoacetic acid. In our attempt to covert the alkyne in intermediate **3.43** to the *trans*-olefin and remove the PMB protecting group under dissolving metal reduction conditions, we did not obtain desired intermediate **3.44**. The reaction conditions not only resulted in our desired transformations but also the cleavage of the ester groups. Due to the cleavage of the acetyl esters, we abandoned our initial route and sought an alternative synthetic route for the synthesis of α-cyanopironetin **3.15**.

3.3.2 Second generation route. While we were originally unsuccessful in synthesizing desired analog **3.15**, we hypothesized we could complete the synthesis by rearranging the functional group transformations from the original route.

3.3.2.1 Retrosynthesis. To avoid late-stage cleavage of the acetate esters during the conversion of the alkyne to the *trans*-olefin in our original route, we proposed a revised route in which the non-conjugated olefin would be introduced prior to the stereoselective Mukaiyama coupling as shown in Scheme 3-13. The updated route maintained our

original synthetic strategy of synthesizing the α-cyano, α,β-unsaturated lactone via an intramolecular Knoevenagel condensation from intermediate **3.45**. Aldehyde **3.45** could be synthesized from previously reported intermediates **3.18, 3.19**, and **3.20** from Keck's pironetin total synthesis utilizing reactions from our original route.[50]

Scheme 3-13. Retrosynthesis of our second generation route for α-cyanopironetin **3.15**

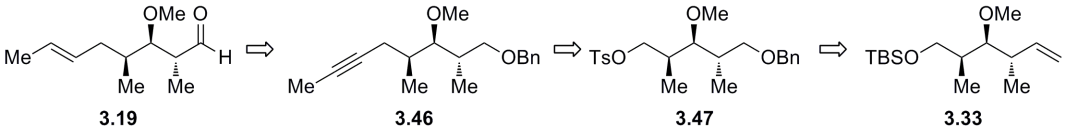


For the synthesis of aldehyde **3.19**, we did not think that our previously utilized route for the synthesis of aldehyde **3.24** could be applied for the synthesis of aldehyde **3.19**. In our original route, aldehyde **3.24** was synthesized via the dihydroxylation and oxidative cleavage of a terminal olefin. Aldehyde **3.19** could not be synthesized from the corresponding terminal olefin due to the presence of the 1,2-disubustituted *trans*-olefin. The dihydroxylation and oxidative cleavage would not be selective between the two olefins since the dihydroxylation with AD-mix-α can occur at both the terminal olefin and the 1,2-disbutituted *E*-olefin.[60] Thus, we sought alternative routes for the synthesis of aldehyde **3.19**.

In our synthetic route for aldehyde **3.19**, we followed a similar strategy used by Keck and coworkers for the synthesis.[50] Similar to Keck's synthesis of aldehyde **3.19**, we proposed the aldehyde could be synthesized from intermediate **3.46** as shown in Scheme 3-14. For the synthesis of alkyne **3.46**, we chose to deviate from Keck's

synthetic route of the common intermediate. We proposed to synthesize the intermediate **3.46** from intermediates from our previous synthesis. The alkyne would be introduced via displacement of the primary tosylate in intermediate **3.47**, which could derived from previously utilized silyl ether **3.33**.

Scheme 3-14. Retrosynthesis of aldehyde **3.19**

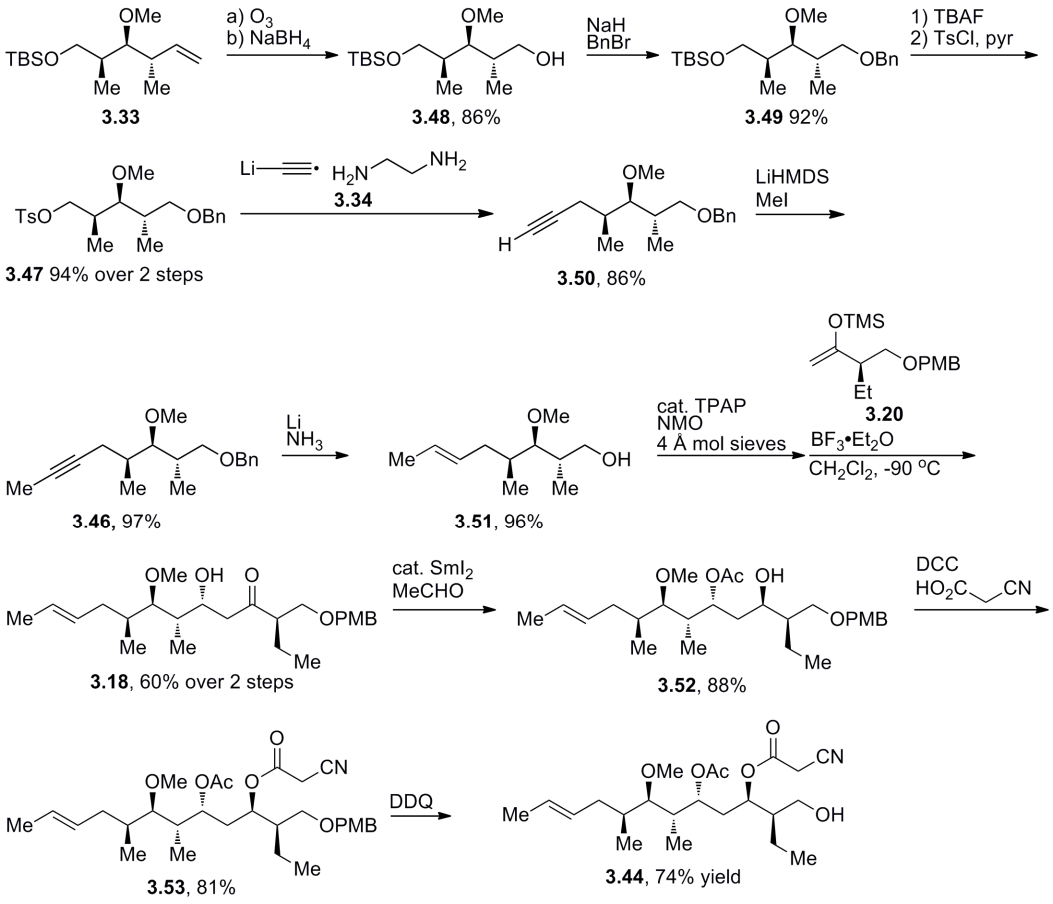


3.19 **3.46** **3.47** **3.33**

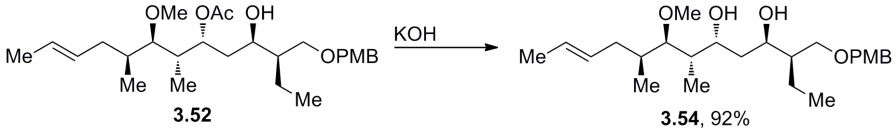
3.3.2.2 Forward synthesis of the carbon-skeleton. The synthesis of aldehyde **3.19** began with the ozonolysis of olefin **3.33** followed by reduction of the intermediate ozonide with $NaBH_4$ to yield the primary alcohol as shown in Scheme 3-15. Primary alcohol **3.48** was subsequently protected as the benzyl ether. The silyl ether in intermediate **3.49** could be converted to intermediate **3.46** following previous reactions for the synthesis of alkyne **3.25**. Under dissolving metal reduction conditions previously reported by Keck and coworkers, the one-pot conversion of the alkyne to the trans-olefin and deprotection of the benzyl ether of intermediate **3.46** resulted in the previously reported primary alcohol **3.51**.[50] The primary alcohol was oxidized to aldehyde **3.19** and reacted with silyl enol ether **3.20** to give previously reported β-hydroxy ketone **3.18**.[50] Intermediate **3.52** was synthesized from β-hydroxy ketone **3.18** following samarium-catalyzed Evans-Tischenko disproportionation reaction with acetaldehyde. The relative configuration of the secondary alcohol from the disproportionation reaction was confirmed following hydrolysis of the acetate ester **3.52** to previously reported diol **3.54** as shown in Scheme 3-16.[50] We completed the synthesis of the desired intermediate **3.44**

following DCC coupling of the secondary alcohol of intermediate **3.52** and DDQ removal of the PMB ether.

Scheme 3-15. Synthesis of the carbon skeleton of analog **3.15**



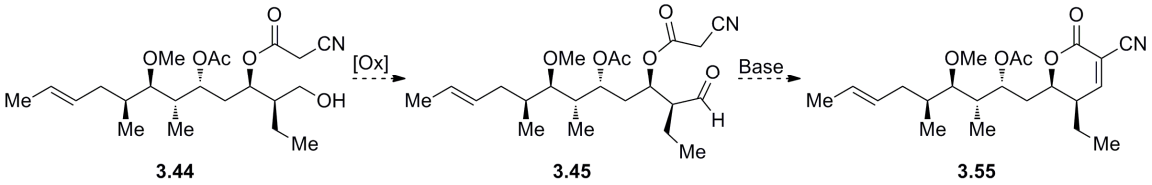
Scheme 3-16. Hydrolysis of ester **3.52** to previously reported diol **3.54**



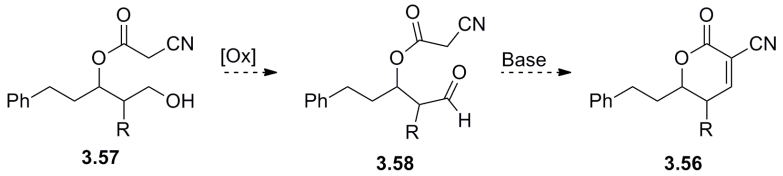
3.3.2.3 Model systems to evaluate the intramolecular Knoevenagel condensation. Following the synthesis of the carbon skeleton of the desired α-cyanopironetin analog **3.15**, we needed to evaluate conditions for both the oxidation of intermediate **3.44** to aldehyde **3.45** and the subsequent Knoevenagel condensation for the synthesis of α-

cyano-α,β,-unsaturated lactone **3.55** (Scheme 3-17). Since both reactions would need to be optimized, we chose to screen reaction conditions for the synthesis of α-cyano-α,β,-unsaturated lactone **3.56** from model substrate **3.57** (Scheme 3-18).

Scheme 3-17. Reaction scheme for the oxidation/Knoevenagel condensation of intermediate **3.44**

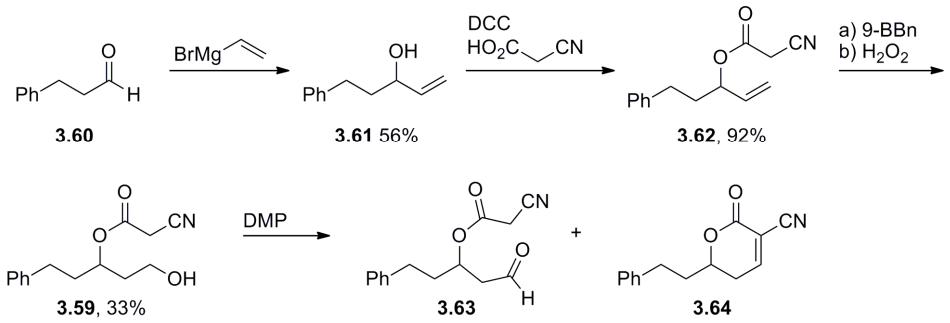


Scheme 3-18. Reaction scheme for the oxidation/Knoevenagel condensation of model substrates

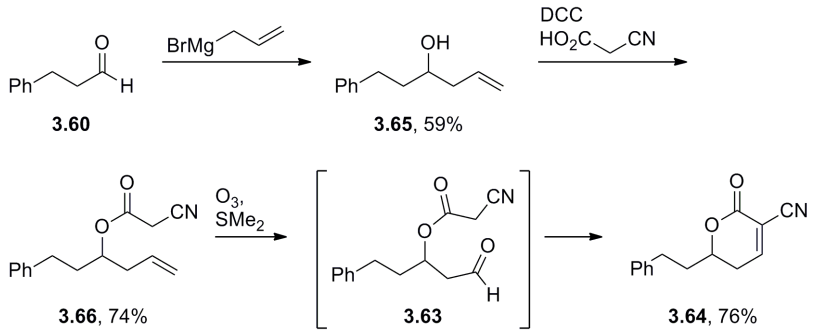


3.3.2.3.1 First generation model substrate. We initially synthesized model substrate **3.59** over 3 steps from aldehyde **3.60** as shown in Scheme 3-19. Following vinyl Grignard addition into aldehyde **3.60**, the resulting secondary alcohol was coupled with cyanoacetic acid to give intermediate **3.62**. Hydroboration of olefin **3.62** resulted in the desired model substrate. During our screen of different oxidants for the conversion of alcohol **3.59** to aldehyde **3.63**, we found that Dess-Martin periodinane oxidation of alcohol **3.59** resulted in the synthesis of desired aldehyde along with the α-cyano, α,β-unsaturated lactone condensation product **3.64**. These results suggested that the intramolecular Knoevenagel condensation of aldehyde **3.63** could occur under mild conditions.

Scheme 3-19. Synthesis of first generation model substrate **3.59** and subsequent oxidation/Knoevenagel condensation



Scheme 3-20. Knoevenagel condensation of aldehyde **3.63** under ozonolysis conditions

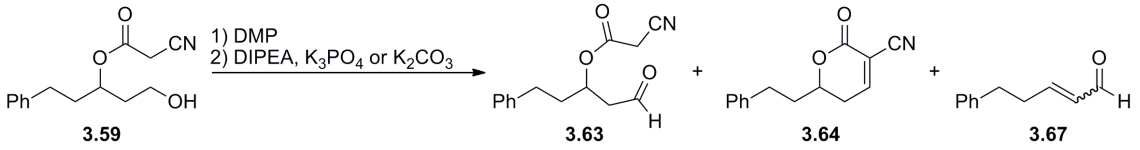


The facile intramolecular condensation was not unexpected since the aldehyde was not isolated in our previous attempts to synthesize aldehyde **3.63**. In an earlier synthesis of aldehyde **3.63** to evaluate conditions for the intramolecular Knoevenagel condensation, we attempted the synthesis of our desired aldehyde via ozonolysis of olefin **3.66**. Olefin **3.66** was synthesized over 2 steps from aldehyde **3.60** as shown in Scheme 3-20. Instead of isolating aldehyde **3.63**, the ozonolysis resulted in synthesis of α-cyano-α,β-unsaturated lactone **3.64** in good yield following intramolecular condensation of aldehyde **3.63** under the reaction conditions.

To improve upon the oxidation/Knoevenagel condensation of model substrate **3.59**, we attempted to facilitate the Knoevenagel condensation with the addition of an external base. The addition of base following the oxidation of alcohol **3.59** resulted in a mixture of products including α,β-unsaturated aldehyde **3.67** resulting from the β-acetoxy

elimination of aldehyde **3.63** (Scheme 3-21). Although we discovered the desired intramolecular Knoevenagel condensation could occur under mild conditions, we believed our initially screened reaction conditions could not be applied for the synthesis of desired lactone **3.55** due to the generation of a mixture of products.

Scheme 3-21. Intramolecular Knoevenagel condensation of first generation model substrate **3.59** in the presense of a base

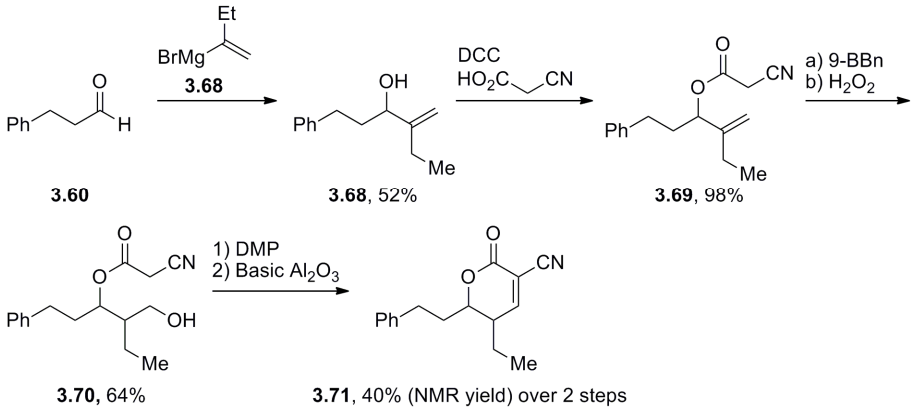


3.3.2.3.2 Second generation model substrate. To improve reaction conditions for the oxidation/Knoevenagel condensation reactions, we hypothesized that the formation of the α,β-unsaturated aldehyde byproduct could be suppressed if the reaction was performed with the more elaborate model substrate, **3.57**, containing an alkyl group along the backbone. The addition of an alkyl group in the model system could decrease the rate of β-acetoxy elimination from aldehyde **3.58**. Screening reaction conditions with model substrate **3.57** containing an alkyl group would also accurately mimic our substrate **3.44** due to the similarities between the two structures.

We completed the synthesis of a second generation model substrate **3.70** containing an ethyl group at the desired position. The synthesis of the updated model substrate was accomplished using the previous synthetic route for the synthesis of model substrate **3.59** as shown in Scheme 3-22. α-Cyano-α,β-unsaturated lactone **3.71** was synthesized in moderate yield following the Dess-Martin periodinane oxidation of model substrate **3.70** and stirring the resulting aldehyde with basic alumina; the potential α,β-

unsaturated aldehyde elimination byproduct was not observed under these reaction conditions.

Scheme 3-22. Synthesis and oxidation/Knoevenagel condensation of second generation model substrate **3.65**



With these updated conditions, we attempted the oxidation/Knoevenagel condensation of our synthetic intermediate **3.44**. Although aldehyde **3.45** was synthesized via Dess-Martin periodinane oxidation of alcohol **3.44**, treatment of the crude aldehyde with basic alumina did not yield desired lactone **3.55**; the primary product observed by ^{1}H NMR analysis of the crude material was the α,β-unsaturated aldehyde **3.72** as shown in Scheme 3-23. Although the α-cyano-α,β-unsaturated lactone **3.71** was synthesized under these conditions, we hypothesized that lactone **3.55** was not synthesized due to the different relative configuration of the groups of intermediate **3.44** and model substrate **3.70**. The relative configuration of these intermediates could affect the relative rates for the desired Knoevenagel condensation over the observed β-acetoxy elimination.

Scheme 3-23. Oxidation and basic alumina-promoted β-acetoxy elimination of intermediate **3.44**

3.3.2.3.3 Third generation model substrate. Since the relative configuration of model substrate **3.58** can effect the product distribution during the intramolecular Knoevenagel condensation, we chose to rescreen reaction conditions with a third model substrate, **3.73**, containing similar relative configuration as our synthetic intermediate **3.44**. The relative configuration in substrate **3.73** was established via *syn*-selective aldol reaction between methyl propionate (**3.74**) and aldehyde **3.60** under reaction conditions reported by Masamune and coworkers (Scheme 3-24).[65] The reduction of ester **3.75** with LAH resulted in diol **3.76**. The primary alcohol was protected as the PMB ether allowing for selective coupling of the secondary alcohol with cyanoacetic acid to give intermediate **3.78**. The desired model substrate **3.73** was obtained following DDQ removal of the PMB protecting group.

Scheme 3-24. Synthesis of third generation model substrate **3.73**.

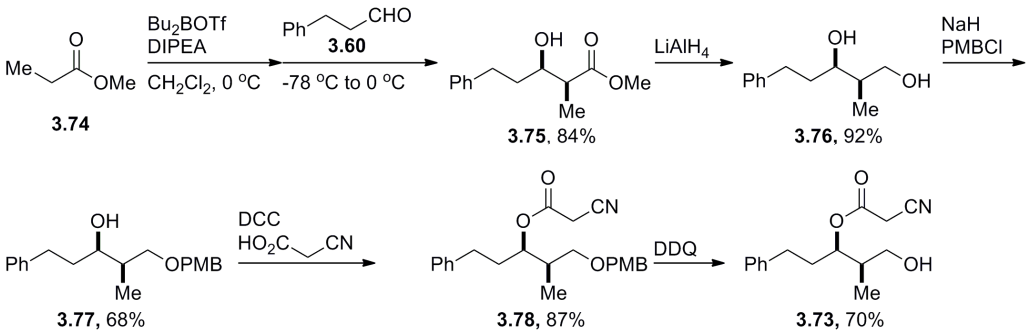
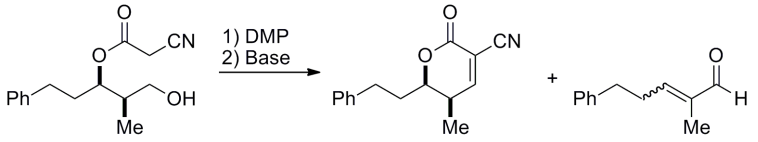


Table 3-3. Screen of bases for the oxidation/Knoevenagel condensation of model subsrate **3.73**



3.73 **3.79** **3.80**

Entry	Base	Condensation Conditions	Yield (**3.79**)	**3.79**:**3.80** Product Ratio[a]
1	Basic Al_2O_3	DCM, RT	25% (NMR yield)	1:1.8
2	KO^tBu	THF, 0 °C to RT	-	-
3	EtO_2C CO_2Et Na	THF, 0 °C	trace	-
4	NaH	THF, -20 °C	35%	30:1

[a] Determined by ^1H NMR spectroscopy of the crude material

We screened a variety of bases for the desired oxidation/Knoevenagel condensation of alcohol **3.73** for the synthesis of lactone **3.79** as shown in Table 3-3. Although we observed the desired lactone following the Knoevenagel condensation in the presence of basic alumina following the oxidation of alcohol **3.73** (Table 3-3, entry 1), the major product was the β-acetoxy elimination byproduct, aldehyde **3.80**. This result is consistent with the observation of α,β-unsaturated aldehyde **3.72** as the product following the oxidation and Knoevenagel condensation of intermediate **3.44** under similar reaction conditions (Scheme 3-23). In addition to basic alumina, we screened other bases for the desired intramolecular condensation. We found sodium hydride to be the optimal base for the desired condensation (Table 3-3, entry 4). Although lactone **3.79** was isolated in low yield, the lactone was synthesized with high preference over the α,β-unsaturated aldehyde **3.80** byproduct.

With our updated Knoevenagel condensation conditions, we attempted to synthesize desired lactone **3.55** to continue the synthesis of desired α-cyanopironetin **3.15**. The DMP-oxidation of intermediate **3.45** and subsequent Knoevenagel

condensation with sodium hydride resulted in the synthesis of the desired lactone as shown in Scheme 3-25.

Scheme 3-25. Synthesis of α-cyano-α,β-unsaturated lactone **3.55**

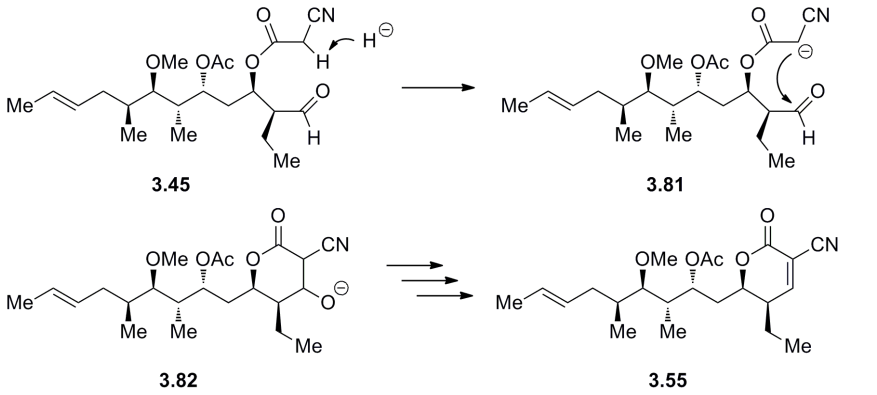
3.45 **3.55**, ~50% of mixture of isomers

Lactone **3.55** was found to epimerize at the γ-position during purification and was isolated as a mixture of diastereomers. We hypothesized that the addition of the nitrile at the α-position increased the acidity of the γ-hydrogen resulting in epimerization under both normal phase and reverse phase column chromatography conditions. We attempted to complete the synthesis of analog **3.15** as a mixture of epimers at the γ-position , but found the hydrolysis of the acetate protecting group of penultimate intermediate **3.55** to be difficult because of the activated Michael acceptor in α-cyano-α,β-unsaturated lactone. Due to the epimerization of the γ-position and challenging late-stage removal of the acetate protecting group in intermediate **3.55**, this route was also abandoned for the synthesis of the α-cyanopironetin **3.15**.

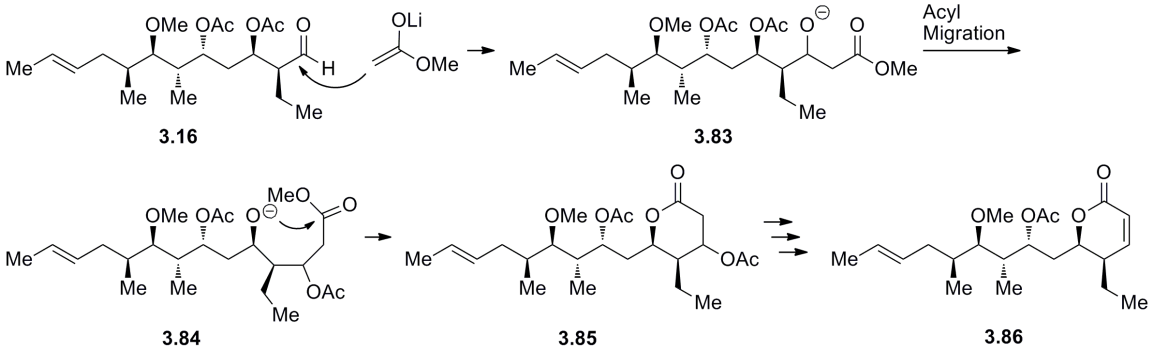
3.4 Synthesis and evaluation of α-functionalized pironetin analogs containing various functional groups. While we were initially unsuccessful with the synthesis of α-cyanopironetin **3.15**, other functional groups such as fluorine or electron-deficient aromatic groups at the α-position of pironetin could also decrease off-target covalent adduct formation. Thus, we chose to synthesize analogs **3.8** containing varying functional groups at the α-position.

3.4.1 Retrosynthesis. Since we proposed to synthesize a series of pironetin analogs **3.8** containing different functional groups at the α-position, we did not believe an intramolecular Knoevenagel condensation could be applied for the synthesis of α,β-unsaturated lactones with varying groups at the α-position. Although our previous synthesis of analog **3.15** used the same retrosynthetic disconnection as Keck for the synthesis of the α,β-unsaturated lactone, the mechanisms for the different reactions used to synthesize the lactone are significantly different.

Scheme 3-26. Mechanism for the intramolecular Knoevenagel condensation of intermediate **3.45**



Scheme 3-27. Mechansim for the synthesis of the α,β-unsatrated lactone from Keck's pironetin total synthesis

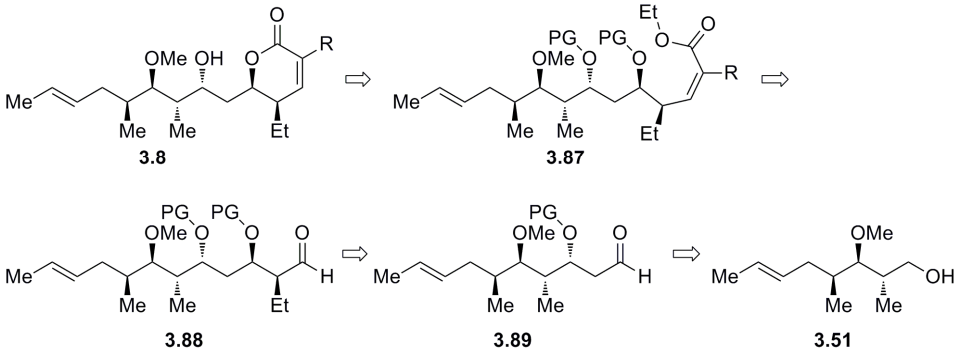


In our synthesis of the α-cyano-α,β-unsaturated lactone **3.55**, we proposed the intramolecular condensation proceeds through a traditional Knoevenagel condensation as shown in Scheme 3-26. In Keck's synthesis for the α,β-unsaturated lactone of pironetin,

the mechanism for the synthesis of the lactone begins with an intermolecular acetate aldol between the lithium enolate of methyl acetate and aldehyde **3.16** as shown in Scheme 3-27.[50,56] The α,β-unsaturated lactone is synthesized following an acyl migration in intermediate **3.83**, lactonization of intermediate **3.84**, and elimination of the β-acetate ester. Due to the different mechanisms for the same retrosynthetic disconnection for the synthesis of α,β-unsaturated lactones **3.55** and **3.86**, a significant amount of optimization of reaction conditions could be required for the synthesis of α-functionalized-α,β-unsaturated lactone of pironetin analogs **3.8** thru a similar retrosynthetic disconnection. Thus, we sought an alternative strategy that could be applied for the synthesis of a variety of α-functionalized-α,β-unsaturated lactones.

In previously reported total syntheses of pironetin, the most common strategy for the synthesis of the α,β-unsaturated lactone is thru an intramolecular lactonization of a *Z*-α,β-unsaturated ester with a hydroxyl group.[45,46,48,49,53,54] We propose to utilize this method for the synthesis of our α–functionalized-α,β-unsaturated lactone in analogs **3.8** as shown in Scheme 3-28.

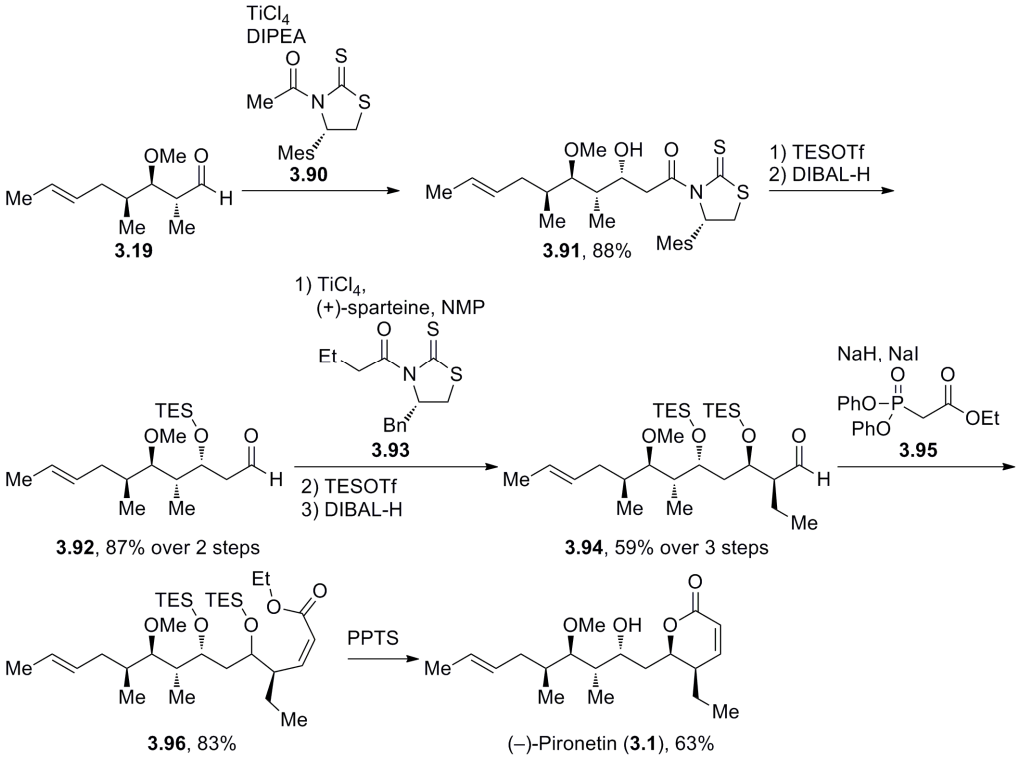
Scheme 3-28. Retrosynthesis of α-funtionalized pironetin analogs



Intermediate **3.87** could be synthesized via a selective olefination of the aldehyde **3.88**. A variety of different olefination conditions have been reported for the synthesis of the

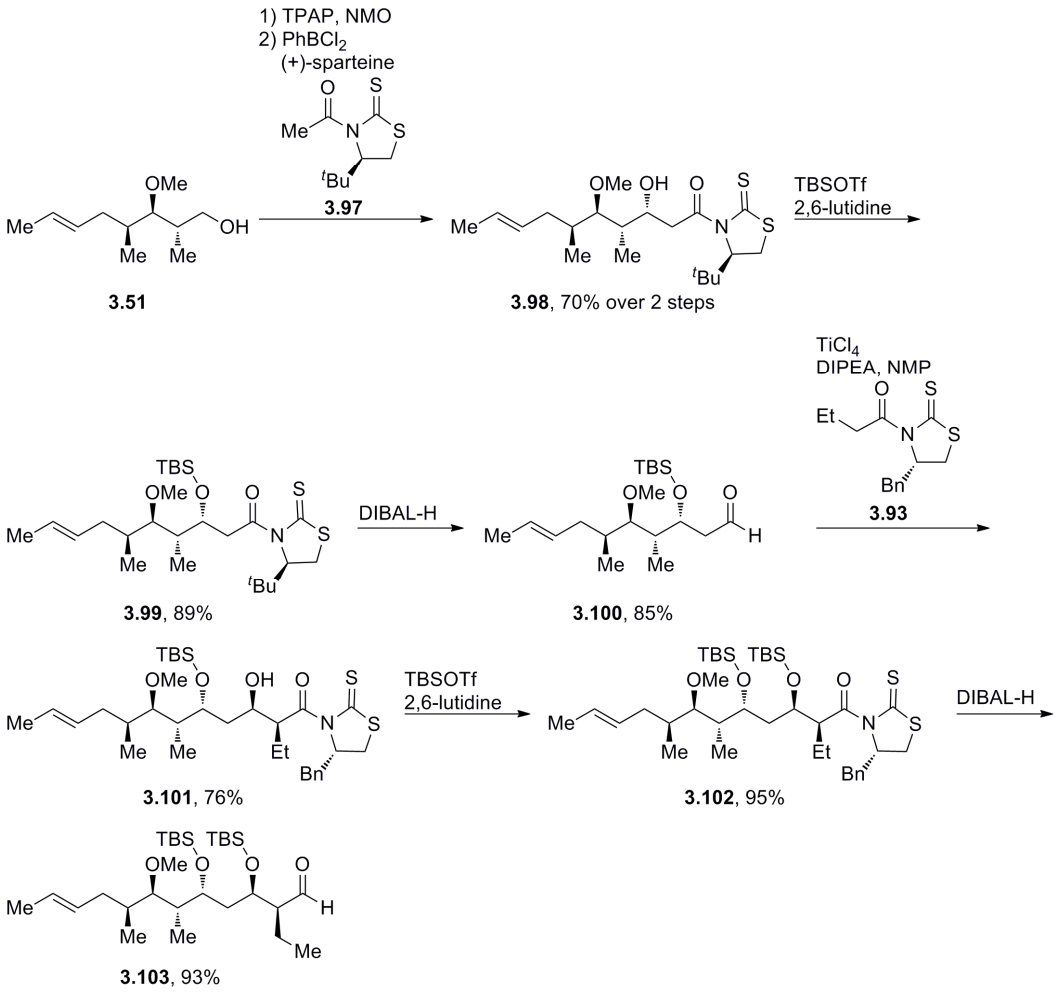
tri-substituted olefin of intermediate **3.87** with the desired olefin geometry; conjugated esters containing halides and alkyl groups at the α-position have been synthesized thru this method.[66-70] Since intermediate **3.88** contains the polyketide backbone of pironetin, we believed this could be synthesized via iterative aldol reactions from previously utilized alcohol **3.51**. A similar iterative aldol/lactonization strategy was utilized by Crimmins and coworkers for the total synthesis of pironetin as shown in Scheme 3-29.[45] The Crimmins group utilized thiazolidinethiones **3.90** and **3.93** for the diastereoselective aldol reactions to synthesize pironetin's polyketide backbone with the appropriate stereochemistry. One advantage of the diastereoselective aldol reactions with thiazolidinethiones over similar Evans oxazolidinones is that thiazolidinethione amides can be converted directly to the corresponding aldehyde, whereas conversion of the oxazolidinone amides to the corresponding aldehydes is performed over two-steps.

Scheme 3-29. Crimmins' total synthesis of pironetin



3.4.2 Forward synthesis. **3.4.2.1 Synthesis of the polyketide backbone**. Similar to Crimmins' synthetic route, the first aldol reaction for the synthesis of the backbone of analogs **3.8** is a stereoselective acetate aldol with aldehyde **3.19**. Conditions for the boron and titanium enolate additions of *N*-acetyl thiazolidinethiones have been reported to occur with high diastereoselectivity.[71-73] The facial selectivity of the acetate addition varies with the reactions conditions for the generation of the enolate. We chose to perform the acetate aldol with *tert*-leucine derived thiazolidinethione **3.97** instead of Crimmins's thiazolidinethione **3.90** since the former thiazolidinethione precursor is readily synthesized from the commercially available unnatural amino acid.[71]

Scheme 3-30. Synthesis of pironetin backbone via iterative aldol reactions



The oxidation of alcohol **3.51** to aldehyde **3.19** and the subsequent addition of the boron enolate of thiazolidinethione **3.97** proceeded in moderate yield to give intermediate **3.98** (Scheme 3-28). Protection of the secondary alcohol as the TBS silyl ether followed by diisobutylaluminum hydride cleavage of the chiral auxiliary resulted in aldehyde **3.100**. A second diastereoselective aldol addition was performed with thiazolidineone **3.93** under similar conditions reported by the Crimmins[45] and Marco[74] groups for synthesis pironetin and related analogs. We completed the synthesis of the polyketide backbone following conversion of intermediate **3.101** to aldehyde **3.103** following previously

utilized conditions for the protection of the secondary alcohol and removal of the chiral auxiliary.

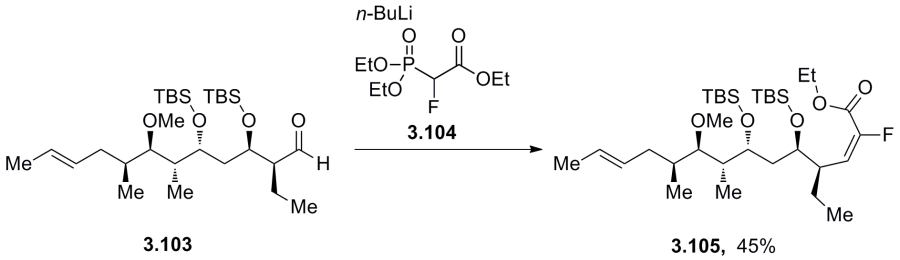
3.4.2.2 Olefination conditions. Although we initially planned to introduce a variety of different groups at the α-position of analogs **3.8** via a diastereoselective olefination of intermediate **3.103**, previous reports on the selective olefination reaction for the synthesis of tri-substituted olefins include the synthesis of α-functionalized conjugated esters containing alkoxides,[75] halides[67-70] or alkyl groups[66] at the α-position. Based on the limited literature precedent, we initially chose to synthesize analogs containing these previously reported groups.

3.4.2.2.1 Olefination with commercially available 2-fluoro-2-phosphonoacetate. Although different olefination regents have been reported for the synthesis of tri-substituted olefins, only one phosphonate ester suitable for our desired olefination reaction was available thru commercial vendors. In 1964, Machleidt and Wessendorf reported the synthesis of *E*-α-fluoro-α,β-unsaturated esters from the olefination reaction with commercially-available triethyl 2-fluoro-2-phosphonoacetate (**3.104**);[68] the commercial availability of the reagent is advantageous for our analog syntheses since the fluorinated analog is one desired analog. Fluorine at the α-position of Michael acceptors has been shown to decrease covalent adduct formation with glutathione.[42]

Following previously reported olefination conditions with phosphonate **3.104**, we synthesized tri-substituted olefin **3.105** from aldehyde **3.103** as shown in Scheme 3-31. While the ^{1}H NMR analysis of the ^{1}H-^{19}F coupling constants[68] of the β-hydrogen of the α,β-unsaturated ester **3.105** in the crude product showed selective synthesis of the desired

E-olefin, the ^{1}H NMR spectrum also showed the presence a second *E*-olefin byproduct. The mixture of products ranged from a 7:1 to 2:1 with the major product being the desired olefin **3.105**. Although the isomers could be separated via silica gel flash chromatography, we proceeded to evaluate alternative olefination conditions for the synthesis of ester **3.105** as a single product.

Scheme 3-31. Olefination with triethyl 2-fluoro-2-phosphonoacetate

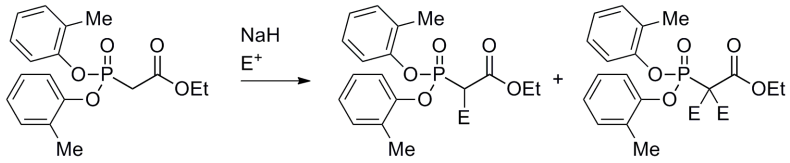


3.4.2.2.2. Synthesis of phosphonate esters. Although only one selective olefination reagent for the synthesis of α-substituted α,β-unsaturated ester was commercially-available, additional phosphonate esters could be synthesized in one or two steps from commercial starting materials. Ando and coworkers previously reported the synthesis of *Z*-α-methyl-α,β-unsaturated esters via the olefination with phosphonate ester **3.101a**.[66] Similar aryl phosphonate esters containing either a bromine or chlorine at the 2-position have utilized for the synthesis of desired *E*-α-halo-α,β-unsaturated esters.[67,69,70] Although the addition of a methyl group, chlorine, or bromine at the α-position of Michael acceptors have not been previously reported to decrease off-target covalent adduct formation, we chose to install these groups at the α-position of analogs **3.8** to evaluate the effect of adding groups with varying electronic properties to the α-position of pironetin.

Due to precedent for the selective olefination with aryl phosphonate esters, we synthesized phosphonate esters **3.106** containing different group at the 2-position from

previously utilized phosphonate ester **3.107** in varying yield (Table 3-4). Quenching the sodium enolate anion of phosphonate **3.107** with electrophilic reagents also resulted in the synthesis of difunctionalized phosphonate esters **3.108** as a byproduct; the disubstituted phonate esters **3.108** were separated from desired phosphonate esters **3.106** via silica gel chromatography.

Table 3-4. Synthesis of functionalized phosphonate esters



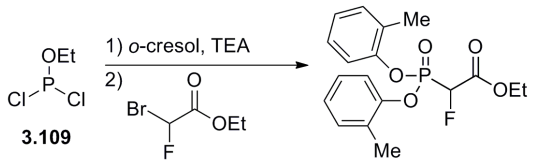
3.107 **3.106** **3.108**

Entry	E^+	Product	E	Product ratio (**3.106**:**3.108**)[a]	Yield
1	MeI	**3.106a**	Me	5:1	55%
2	NCS	**3.106b**	Cl	1:1	30%
3	$BrCl_2CCCl_2Br$	**3.106c**	Br	8:1	55%[b]
4	Selectofluor®	**3.106d**	F	-	12%[c]

[a] Determined by ^{31}P NMR spectroscopy of the crude material
[b] Isolated as a 12:1:1 mixture of **3.106c**:**3.106c**:**3.108c** by ^{31}P NMR spectroscopy
[c] Isolated as a 6.5:1 mixture of **3.101d**:byproduct by ^{31}P NMR spectroscopy

Although the olefination with aryl 2-fluorophosphoante esters has not been reported in the literature, we attempted to synthesize fluorine-containing ester **3.106d** following previously reported methods for the electrophilic fluorination of phosphonate esters;[76] impure phosphonate ester **3.106d** was only obtained in low yield. We were, however, able to synthesize phosphonate ester **3.106d** from phosphite **3.109** as shown in Scheme 3-32. The desired phosphonate ester was synthesized in moderate yield via substitution of the chloro groups of phosphite **3.109** with *o*-cresol and subsequent Arbuzov reaction with ethyl bromofluoroacetate (**3.110**).

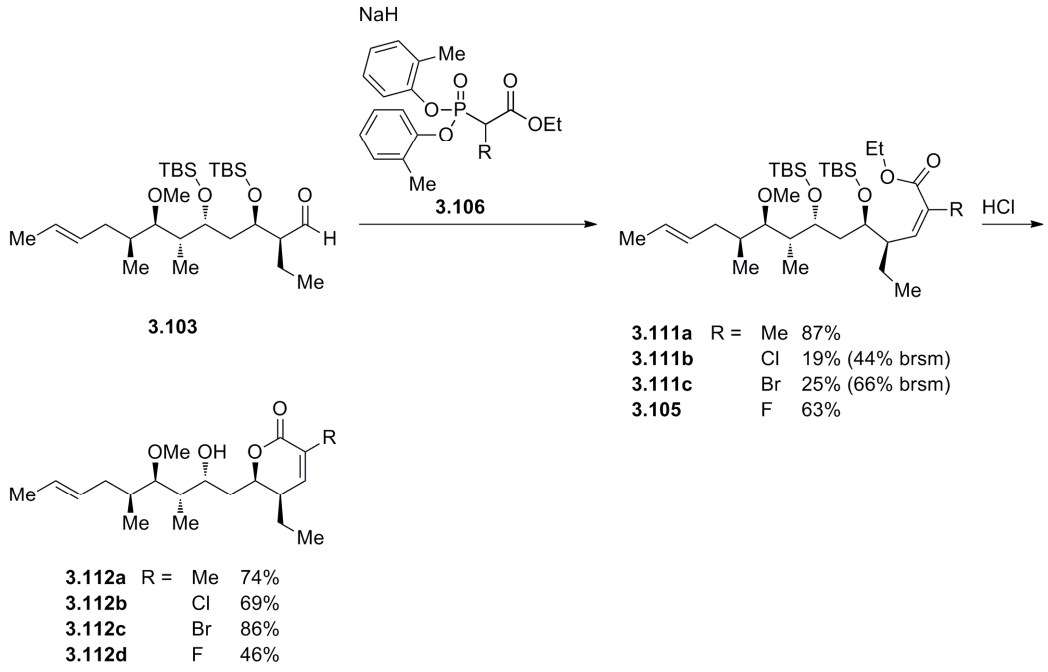
Scheme 3-32. 2-step synthesis of 2-fluorophosphonate ester **3.106d**



3.106d, 41% over 2 steps

3.4.2.3 Completion of the synthesis of the first series of α-functionalized pironetin analogs. Following the synthesis of phosphonate esters **3.106**, we performed the olefination reactions between aldehyde **3.103** and our synthesized phosphonate esters (Scheme 3-33). The desired α-functionalized-α,β-unsaturated esters **3.105** and **3.111** were synthesized in varying yield. The olefination with phosphonate ester **3.106a** proceeded with the highest yield; the relative geometry of the α,β-unsaturated ester in intermediate **3.111a** was confirmed from an observed NOE correlation between the α-methyl group and the β-hydrogen. Although the olefination of the chloro- and bromo-phosphonate esters proceeded in low yield, we were able to recover a significant amount of unreacted aldehyde **3.103**. For the olefination with 2-fluorophosphonate ester **3.106d**, we obtained the α-fluoro-α,β-unsaturated ester **3.105** as a single isomer with the desired *E*-geometry of the conjugated olefin; this was an improvement upon our previous olefination attempt with commercial phosphonate ester **3.104**. Following the olefination reaction, we completed the synthesis our first series of pironetin analogs **3.112** following lactonization of the α,β-unsaturated esters under acidic conditions.

Scheme 3-33. Synthesis of α-functionalized pironetin analogs via olefination and lactionzation reactions

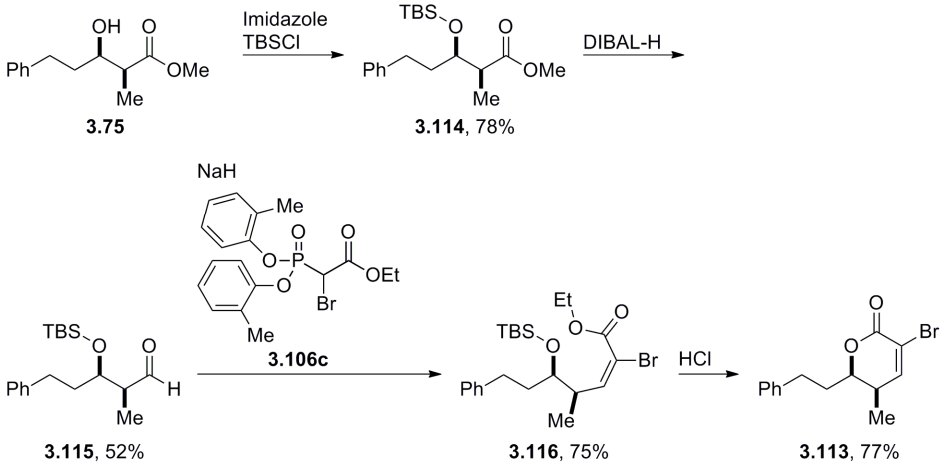


3.4.2.4 Functionalization via cross-coupling with α-bromopironetin. Although we were limited in the different type of the functional groups we could install directly via our olefination strategy, we hypothesized that we could introduce additional functional groups at the α-position via a transition metal catalyzed cross-coupling reaction with α-bromopironetin **3.112c**. We previously proposed to introduce groups via cross-coupling in our earlier proposed semi-synthesis routes for the synthesis of α-functionalized pironetin analogs. Although we could also perform the cross-coupling reaction with α-chloropironetin **3.112b**, we chose to focus on the cross-coupling with analog **3.112c** due to the increased reactivity of vinyl bromides over vinyl chlorides. In addition to the coupling with aromatic nucleophiles via a Stille, Suzuki, or Negeshi coupling, a wide variety groups could be installed via a transition-metal cross-couplings reaction since methods have been reported for the conversion of aryl or vinyl bromides to a variety of

groups such as an aniline,[77] phenol,[78] ester,[77] amide,[77] nitrile,[79] or CF_3 group.[80-82] However, a number of these methods require harsh reaction conditions such as elevated temperatures or the addition of a strong base. These conditions could potentially result in the decomposition of analog **3.112c** and/or epimerization at the γ-position of the α,β-unsaturated lactone during the cross-coupling reaction.

3.4.2.4.1 Cross-coupling model substrate synthesis. Due to the numerous published cross-coupling reaction conditions and the limited amount of α-bromopironetin **3.112c**, we chose to evaluate potential cross-coupling conditions with model substrate **3.113** containing a α-bromo-α,β-unsaturated lactone. As shown in Scheme 3-34, the model substrate was synthesized via an analogous olefination/lactonization route utilized for the synthesis of our pironetin analogs. β-Hydroxy ester **3.75** was converted to aldehyde **3.115** following protection of the secondary alcohol and reduction of the methyl ester to the corresponding aldehyde. Olefination and subsequent lactonization under previously utilized conditions resulted in the synthesis of model substrate **3.113**.

Scheme 3-34. Synthesis of cross-coupling model substrate **3.113**



3.75

3.114, 78%

3.115, 52%

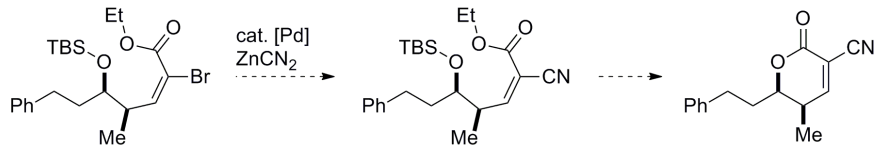
3.116, 75%

3.113, 77%

3.4.2.4.2 Cyanation cross-coupling. One of the initial groups we sought to install via a cross-coupling reaction was a nitrile. We had been unsuccessful in the synthesis of α-cyano analog **3.15** from previous routes, and hypothesized that the cross-coupling between vinyl bromides **3.111c** or **3.112c** and cyanide could be an alternative route for the synthesis of the desired analog. The palladium-catalyzed coupling between aryl halides and zinc cyanide has been reported to occur at ambient temperature in the presence additional zinc metal.[83] Cyanation reactions have been reported with palladium catalysts containing P^tBu_3 as a ligand. Researchers at AstraZeneca previously utilized the $[(^tBu)_3PPdBr]_2$ complex as a precatalyst for the cyanation of aryl bromides for the synthesis of an active pharmaceutical ingredients.[84]

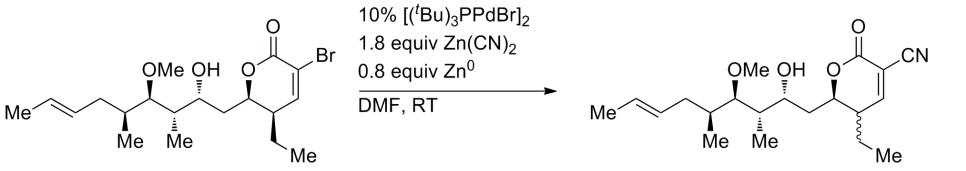
Although we synthesized model substrate **3.113**, initial studies into the cyanation coupling reaction were performed with α-bromo-α,β-unsaturated ester **3.116**. We proposed that following the coupling of vinyl halide **3.116** with zinc cyanide, we could complete the synthesis of the α-cyano, α,β-unsaturated lactone **3.117** following lactonization of cross-coupling product **3.118** as shown in Scheme 3-35. If this route was successful, we could apply our reaction conditions for the synthesis of α-cyanopironetin **3.15** from vinyl halide **3.111c**. Following previously reported cyanation conditions, the coupling of **3.111** with 1.8 equiv zinc cyanide catalyzed by 5% $[(^tBu)_3PPdBr]_2$ in the presence of 0.12 equivalents Zn metal resulted in intermediate **3.118** in 87% yield. Although the cyanation coupling proceeded in high yield, we were unable to cyclize α-cyano-α,β-unsaturated ester **3.118** to lactone **3.117** even in the presence of a Brønsted or Lewis acid.

Scheme 3-35. Cyanation/lactonization route for the synthesis of α-cyano-α,β-unsaturated lactones



3.116 **3.118** **3.117**

Scheme 3-36. Synthesis of α-cyano analog **3.15** via cyanation reaction

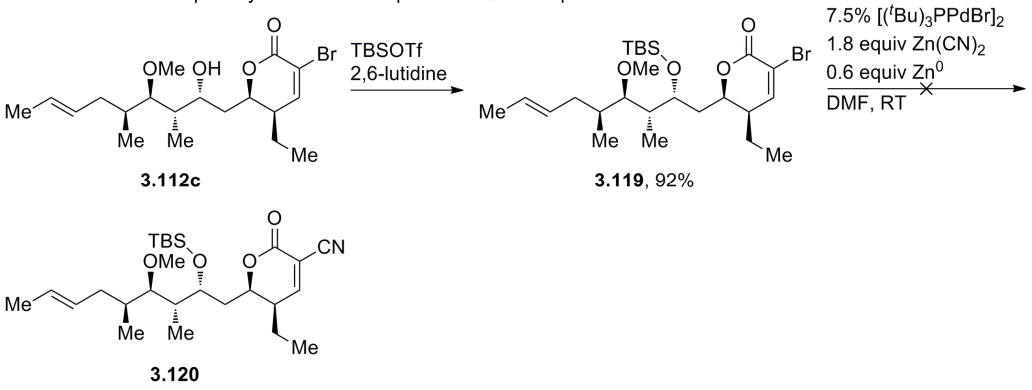


3.112c **3.15**, 66% (90% brsm) as a mixture of isomers

Although we couldn't synthesize the desired α-cyano-α,β-unsaturated ester **3.117**, the successful coupling of vinyl halide **3.116** with zinc cyanide suggested we could synthesize the α-cyanopironetin **3.15** via a palladium catalyzed cyanation reaction. We attempted the cyanation with α-bromopironetin **3.112c** under similar reaction conditions as shown in Scheme 3-36. α-Cyanopironetin **3.15** was obtained in moderate yield as mixture of products. Although epimerization at the γ-position was foreseen from our previous attempts to synthesis analog **3.15**, additional inseparable byproducts were generated under the reaction conditions. We hypothesized that these additional byproducts could be due to side reactions between the secondary alcohol of α-bromopironetin **3.112c** and the palladium catalyst. We subsequently protected the secondary alcohol of α-bromopironetin **3.112c** as the TBS ether and submitted vinyl halide **3.119** to similar cyanation conditions as shown Scheme 3-37. To our surprise, only trace amounts of coupling product **3.120** were observed. Due to requirement for additional optimization of cyanation conditions of either vinyl halide **3.112c** or **3.119** and

the epimerization at the γ-position of α-cyano-α,β-unsaturated lactones, we abandoned the synthesis of analog α-cyanopironetin **3.15** altogether.

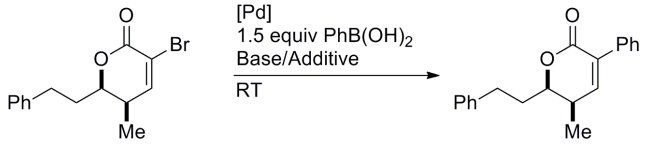
Scheme 3-37. Attempted cyanation of TBS-protected α-bromopironetin **3.119**



3.4.2.4.3 Suzuki cross-coupling. Since Taunton and coworkers had reported that the Michael acceptors containing electron-deficient aromatic groups at the α-position were also reversible covalent inhibitors, we hypothesized that α-aryl pironetin analogs could also have decreased off-target covalent adduct formation.[41] These analogs could be readily synthesized via cross-coupling reaction between α-bromopironetin **3.112c** and an aryl nucleophile. Although various aryl nucleophiles could be utilized for the cross-coupling reactions, we focused on exploring Suzuki couplings with an arylboron reagent due to the commercial-availability and functional-group tolerance of these reagents. Various catalysts and reaction conditions have been reported for the Suzuki coupling of aryl halides under mild conditions. Our initial survey of various Suzuki coupling conditions focused on catalyst and reaction conditions that occur at room temperature and did not require the addition of a strong base. Fu and coworkers previously reported the $Pd_2(dba)_3/P^tBu_3$ catalyzed coupling of aryl bromide with boronic acid at room temperature in the presence of potassium fluoride as a base.[85] More recently, Buchwald

and coworkers reported the coupling of aryl halides with fluorinated boronic acids at room temperature in the presence of potassium phosphate catalyzed by cyclometalled Xphos Pd G2 complex.[86] Based on these two reports, we screened previously reported Suzuki coupling conditions utilizing either Pd/P^{t}Bu$_3$[85,87,88] or Pd/Xphos[86] catalysts for the coupling of model substrate **3.113** with phenyl boronic acid as shown in Table 3-5.

Table 3-5. Screen of Suzuki coupling conditions of model system **3.113**



3.113 **3.121**

Entry	[Pd]	Base/Additive	Solvent	Reaction Time	Yield[a]	ref
1	10% [(^{t}Bu)$_3$PPdBr]$_2$	4.5 equiv KF	THF	1	trace	84
2	5% [(^{t}Bu)$_3$PPdBr]$_2$	4.5 equiv KF, 2 equiv H_2O	THF	5.5 h	94%	87
3	5% [(^{t}Bu)$_3$PPdBr]$_2$	1.65 equiv K_3PO_4	THF:MeCN;H_2O	3 h	74% (95%[b])	86
4	10% Xphos Pd G2	2 equiv K_3PO_4	THF:H_2O	3 h	76%	85

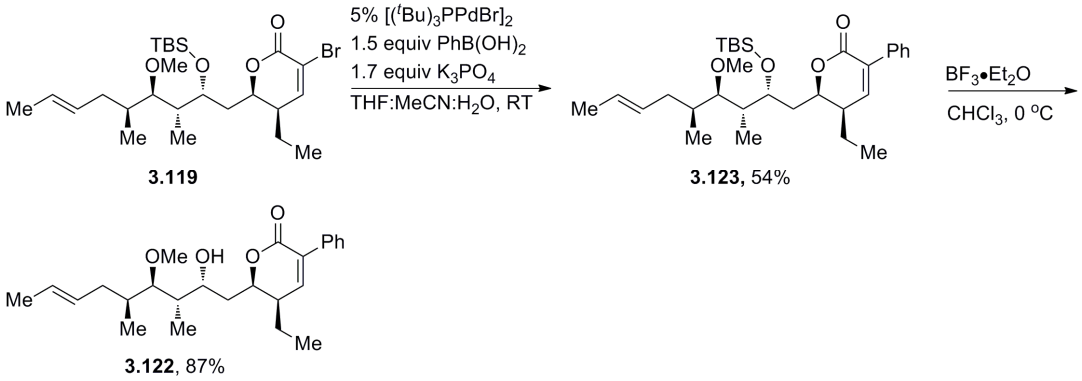
[a] NMR yield based

[b] Isolated yield

The α-phenyl-α,β-unsaturated lactone **3.121** was synthesized in high yield under various reaction conditions in which water was either an additive or a co-solvent. We chose to proceed with the [(^{t}Bu)$_3$PPdBr]$_2$ catalyzed coupling in the presence of potassium phosphate in a water:acetonitrile:THF solvent mixture due to the high yield and short reaction time (Table 3-5, entry 3). Reactions catalyzed by [(^{t}Bu)$_3$PPdBr]$_2$ also did not show additional byproducts associated with the palladium precatalyst complex unlike the Xphos Pd G2 catalyst (Table 3-4, entry 4). Since we hypothesized that the free hydroxyl group in α-bromopironetin **3.112c** could result in undesired side reactions and/or catalyst decomposition, we chose to apply our optimized Suzuki coupling conditions for the coupling of TBS-protected α-bromo-α,β-unsaturated lactone **3.119** with phenylboronic acid. Although Taunton and coworkers only evaluated the effect of an electron-deficient

aromatic group at the α-position of Michael acceptors,[41] we chose to synthesize the α-phenylpironetin **3.122** to initially evaluate if aryl groups would be tolerated at the α-position of pironetin. The desired Suzuki coupling reaction proceeded in moderate yield as shown in Scheme 3-38. We completed the synthesis of our desired analog following removal of the TBS protecting group in intermediate **3.123** with $BF_3 \bullet Et_2O$.

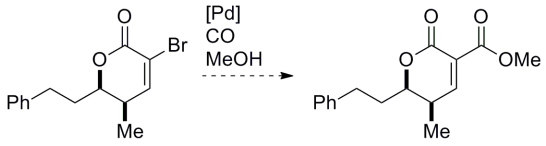
Scheme 3-38. Synthesis of α-phenylpironetin **3.122**



3.4.2.4.4 Additional cross-coupling reactions. Along with introducing a nitrile and aromatic group at the α-position of pironetin via a cross-coupling reaction, we were interested in installing other groups at the α-position with similar electronic properties as the nitrile. Two groups we proposed to introduce through cross-coupling reactions were either an ester or amide. We proposed to introduce these groups via a carbonylation reaction of vinyl halide **3.119** in the presence of either an alcohol or amine under a carbon monoxide atmosphere. To evaluate the possibility of converting an α-bromo-α,β-unsaturated lactone to an α-carbonyl-α,β-unsaturated lactone, we evaluated the carbonylation reaction of model substrate **3.113** with methanol as shown in Scheme 3-39. We screened a variety of palladium catalysts previously reported for the carbonylation of aryl halides under atmospheric pressure of carbon monoxide.[89-92] We did not obtain

desired ester **3.124** under screened conditions with either Pd/dppe or Pd/Xantphos catalyst systems. These preliminary results suggested that further optimization of the carbonylation reaction conditions is required for the synthesis of α-carbonyl-pironetin analogs from vinyl bromide **3.119**.

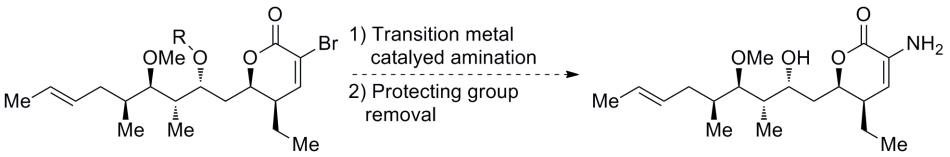
Scheme 3-39. Attempted carbonylation reaction of **3.113**



3.113 **3.124**

Although we initially-focused on the addition of electron-deficient groups at the α-position of pironetin to decrease off-target covalent adduct formation, we became interested in evaluating the effect of an electron-donating group at this position to further explore the SAR at this position. Thus, we chose to explore the synthesis of α-aminopironetin **3.125** via coupling of vinyl bromide **3.119** with an ammonia source as shown in Scheme 3-40.

Scheme 3-40. Potential route for the synthesis of α-aminopironetin **3.125**



3.112c R = H
3.119 TBS

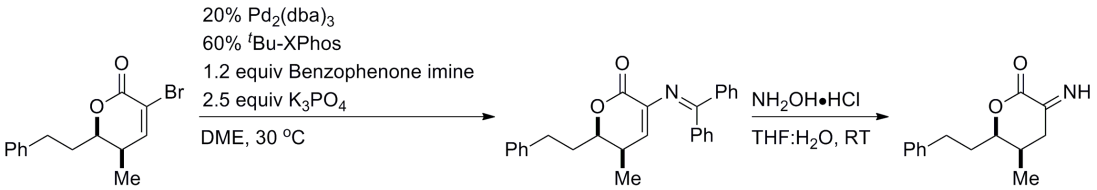
3.125

Although the transition-metal catalyzed coupling of aryl bromides with ammonia has been reported in the literature, these reactions require high temperature and the addition of a strong base such as sodium *tert*-butoxide.[93,94] Thus, we chose to explore the coupling of vinyl bromide **3.119** with an ammonia surrogate, which have been reported to occur under milder conditions. Hartwig and coworkers previously reported the Pd/P^{t}Bu$_3$-

catalyzed coupling between aryl halides with $Zn(HMDS)_2$ as the ammonia surrogate for the synthesis of anilines at either ambient temperature or 45 °C. $Zn(HMDS)_2$ could be generated *in situ* from commercial solutions of $ZnCl_2$ and LiHMDS.[95] Researchers at GlaxoSmithKline had also reported the synthesis of anilines via Pd/^{t}Bu-Xphos-catalyzed coupling of aryl bromides with the ammonia surrogate, benzophenone imine, in the presence of potassium phosphate at 30 °C.[96]

We initially explored the Pd/P^{t}Bu$_3$-catalyzed amination of model substrate **3.113** with *in situ* generated $Zn(HMDS)_2$ but we did not observe the desired coupling product from these reactions and only recovered unreacted starting material. We subsequently explored the coupling of our model substrate with benzophenone imine as shown in Scheme 3-41. Even under previously reported amination conditions, we did not observe the synthesis of imine **3.126** in yields greater than two turnovers of the catalyst even with 40% palladium catalyst. Although imine **3.126** was obtained in low yield, we found the imine could be hydrolyzed in the presence of hydroxylamine hydrochloride; hydrolysis of the benzophenone imine **3.126** resulted in imine **3.127** instead of the conjugated enamine isomer.

Scheme 3-41. Amination of model substrate **3.113**

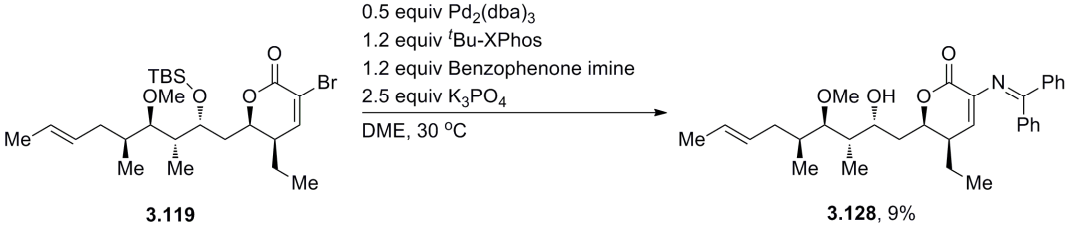


3.113 **3.126**, 50% (NMR yield) **3.127**, 57%

Although the coupling with benzophenone imine and subsequent hydrolysis did not occur in high yield, we attempted these reactions with TBS-protected α-bromo-α,β-unsaturated

lactone **3.119** as shown in Scheme 3-42. Due to the low-catalyst turnover in the coupling with model system **3.113**, the amination reaction was attempted with stoichiometric amount of palladium and ligand to potentially increase the yield of the desired coupling product. However, the desired imine product **3.128** was only isolated in 9% yield. Due to the low yield of the amination product under these conditions, further optimization of the amination reaction conditions is required for the coupling of α-bromo-α,β-unsaturated lactone with an ammonia surrogate. Thus, we chose to postpone the synthesis of the α-amino analog **3.125** via the amination route of vinyl bromide **3.119**.

Scheme 3-42. Amination of TBS-protected α-bromopironetin **3.119**

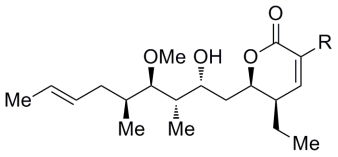


3.119 **3.128**, 9%

3.4.3 Biological activity. Following the synthesis of our α-functionalized pironetin analogs, we investigated their biological activity to evaluate the structure-activity relationship of the α-position. The antiproliferative activity was evaluated in a drug-sensitive OVCAR5 ovarian cancer cell line, drug-sensitive A2780 ovarian cancer cell line along with the cisplatin-resistant A2780-CP ovarian cancer cell line (Table 3-6). The addition of a group at the α-position of pironetin resulted in decreased antiproliferative activity. While the addition of a methyl group to the α-position of pironetin (Table 3-6, entry 4) resulted in an approximate 200-fold decrease in biological activity, the α-phenyl analog **3.122** was found to be inactive (Table 3-6, entry 8). The α-methyl, α-chloro, and α-fluoro analogs (Table 3-6, entries 4-5 and entry 7) were calculated to have similar GI_{50}

values even though these groups have different electronic properties; these results suggest the decreased biological activity of our α-functionalized analogs was primarily due to the steric properties of the group at the α-position instead of the electronic properties of the various groups. Although α-cyanopironetin analog **3.15** was synthesized as a mixture of products, we chose to evaluate the antiproliferative activity of the mixture; the mixture was found to be inactive in our assay (Table 3-6, entry 3).

Table 3-6. Antiproliferative activity of α-functionalized pironetin analogs



			GI_{50} (μM)[a]		
Entry	Compound	R	OVCAR5[b]	A2780[b]	A2780-CP[c]
1	Paclitaxel	-	0.0210 ± 0.0020	0.00753 ± 0.00157	0.00973 ± 0.00130
2	Pironetin (**3.1**)	H	0.0144 ± 0.0008	0.0243 ± 0.0009	0.0173 ± 0.0004
3	**3.15**[d]	CN	>30	>30	>30
4	**3.112a**	Me	3.63 ± 0.16	10.2 ± 0.4	9.12 ± 1.12
5	**3.112b**	Cl	1.08 ± 0.07	4.48 ± 0.02	3.62 ± 0.10
6	**3.112c**	Br	0.0684 ± 0.002[e]	0.901 ± 0.074	0.281 ± 0.015
7	**3.112d**	F	3.24 ± 0.07	5.11 ± 0.36	4.46 ± 0.15
8	**3.122**	Ph	>50	>50	>50

[a] Average of 2 experiments performed in triplicate ± SEM (n = 6)
[b] Drug-sensitive ovarian cancer cell line
[c] Cisplatin-resistant ovarian cancer cell line
[d] Evaluated as an impure mixture of γ-epimers and byproducts
[e] Calculated from fitting a sigmoidal standard dose-response cruve to a biphasic graph

Although our α-functionalized pironetin analogs were found to have decreased biological activity relative to the natural product, α-bromopironetin **3.112c** had unique activity (Table 3-6, entry 6). While analog **3.112c** had sub-micromolar GI_{50} values against all three cell lines, the dose response curves suggest the analog may act through an alternative mechanism of action (Figure 3-3). In the OVCAR5 cell lines, the dose response curve for α-bromopironetin **3.112c** showed biphasic character; this was not

observed in the A2780 cell lines or with any of our other tubulin-binding agents including pironetin and our synthesized analogs in either cell lines.

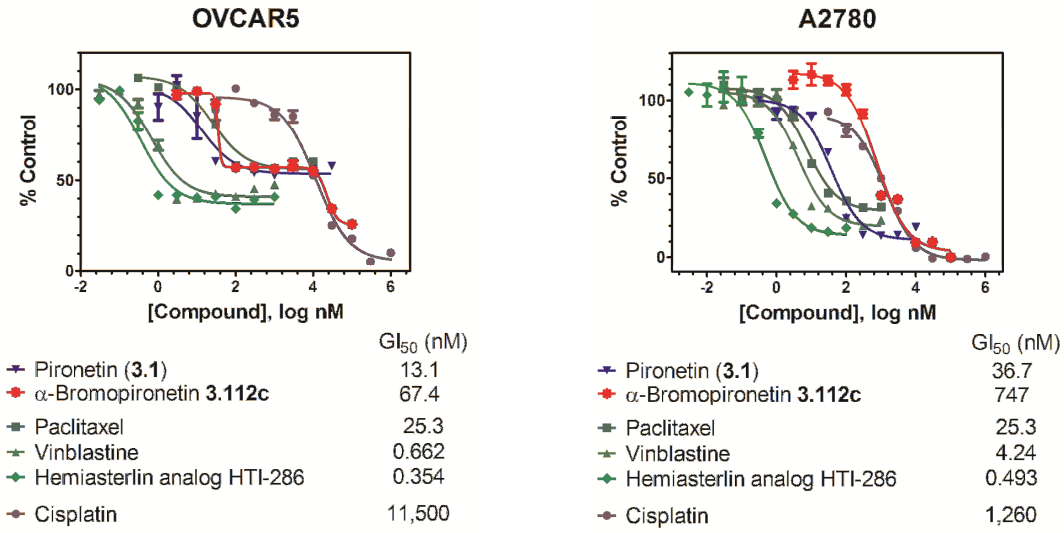


Figure 3-3. Representative dose-response curves of α-bromopironetin **3.112c** and other chemotherapeutic agents.

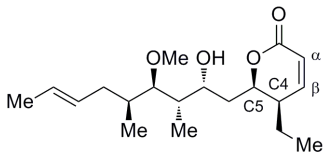
Another interesting aspect for the dose-response curves of α-bromopironetin **3.112c**, was the percentage of cells remaining at the high drug concentrations. In the dose-response curves of tubulin-binding agents paclitaxel, vinblastine, and pironetin in the A2780 cell line, the dose-response curve plateaus at approximately 10% to 30% of the control population at the higher tested drug concentrations. In the dose response curves of α-bromopironetin **3.112c** in the A2780 cell line, the highest doses of the analog resulted in <10% of the control population; this was significantly lower than other evaluated tubulin-binding agents. The only compound we previously evaluated which resulted in similar levels of the cell population remaining at the high drug doses was cisplatin. Cisplatin's mechanism of action does not involve the binding to tubulin, but involves forming crosslinks within DNA. Similar activity of α-bromopironetin **3.112c** was observed in the dose-response curve in the OVCAR5 cell line albeit to a lower

extent. Due to the similar degree at which α-bromopironetin **3.112c** and cisplatin can decreases cell population at high doses along with its bimodal dose-response curve in the OVCAR5 cell line, we hypothesize α-bromopironetin analog **3.112c** may have an alternative and/or additional mechanism of action other than binding to α-tubulin.

3.5 Conclusion. Based on previous studies on the effect of functional groups at the α-position of Michael acceptors, we sought to synthesize α-functionalized pironetin analogs with the goal of decreasing the natural product's off-target covalent adduct formation. The structure-activity relationship at this position had not been previously reported in the literature. Although our initial attempts to synthesis α-cyanopironetin **3.15** via total synthesis were unsuccessful, we completed the synthesis of an initial series of analogs containing either a halogen or methyl group at the α-position. Additional groups at the α-position were introduced following cross-coupling reaction with either the α-bromo analog **3.112c** or **3.119**. The addition of a functional group at the α-position of pironetin resulted in significant decreased antiproliferative activity of at least 100-fold for the majority of our analogs. However, α-bromopironetin **3.112c** was found to have only a 10-40 fold decrease in biological activity relative to pironetin. This increased activity of analog **3.112c** relative to our other α-functionalized pironetin analogs could be due to the analog acting through a different mechanism(s) of action in addition to binding to α-tubulin. Further studies are required to identify potential mechanisms of action of this analog. Due to the overall lower biological activity of our synthesized analogs, we chose not the further evaluate the effect of the functional group at α-position of pironetin upon the off-target covalent-adduct formation of the natural product.

CHAPTER 4. EVALUATION OF THE STRUCTURE-ACTIVITY RELATIONSHIP OF THE C4- AND C5-POSITIONS OF THE α,β-UNSATURATED LACTONE OF (-)-PIRONETIN

4.1 Introduction. During our previous studies on the SAR of the α-position of pironetin (Figure 4-1, **4.1**), we observed epimerization at the C4-position upon addition of a nitrile at the α-position. Due to this observation, we became interested in evaluating the structure-activity relationship at other positions of the α,β-unsaturated lactone of pironetin. While a number of total syntheses of the natural product have been reported, few reports have evaluated the SAR at the various positions of the lactone.



(–)-Pironetin (**4.1**)

Figure 4-1. Structure and positions of pironetin.

Previously reported pironetin analogs containing modification at different positions of the lactone are shown in Figure 4-2. Kitahara and coworkers reported that analog **4.2** containing a saturated lactone showed a 1000-fold decrease in biological activity in microtubule disassembly assays compared to the natural product.[97] The decreased activity of this analog would be expected since pironetin's mechanism of action involves the Michael addition of cysteine 316 into the α,β-unsaturated lactone. Vogt and coworkers reported that the addition of a hydroxyl group to the β-position of the unsaturated lactone (**4.3**) results in a 10-75 fold decrease in antiproliferative activity in various cancer cell lines.[31] Qing and coworkers synthesized gem-difluorinated analog **4.4** and the corresponding C5-epimer *epi*-**4.4**.[98] The GI_{50} values for these analogs were

measured at 600 to 1500 nM against MGC803 and A375 cancer cell lines respectively. More recently, Marco and coworkers have synthesized simplified pironetin analogs **4.5** and evaluated the structure-activity relationship at the C4- and C5-position of their simplified scaffold.[28,74] The group hypothesized that the C4-ethyl group is necessary for biological activity since analog **4.5c** had a GI_{50} value of 10 μM in A2780 ovarian cancer cell line whereas methyl analog **4.5b** was found to be inactive with a GI_{50} value >200 μM. Analogs **4.5a** and ***epi*-4.5a** were found to have comparable GI_{50} values of 22.9 μM and 44 μM respectively; these results suggest the stereochemistry at the C5-position did not significantly influence the biological activity of their analogs.

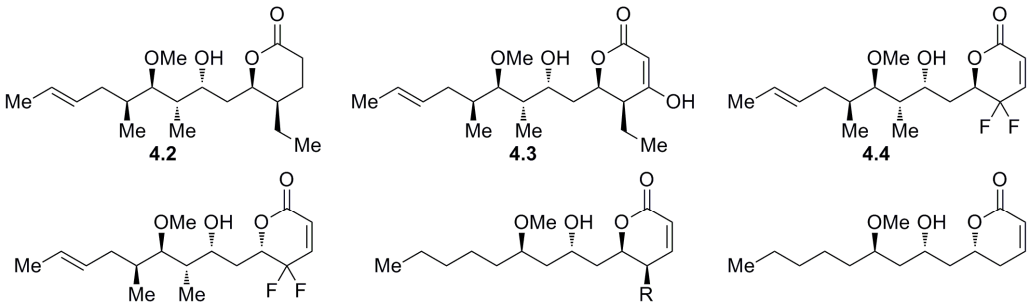


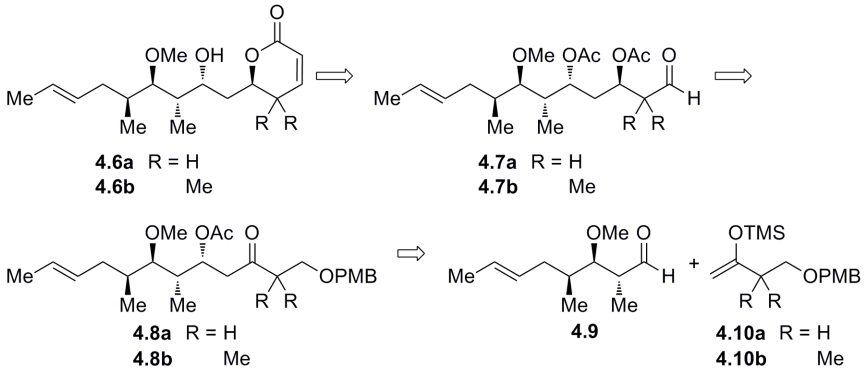
Figure 4-2. Structure of previously reported pironetin analogs with modification at the α,β-unsaturated lactone.

We hypothesized that the groups and stereochemistry at the C4- and C5-positions of pironetin could play keys roles in the binding of pironetin to α-tubulin prior to covalent adduct formation, and thus chose to focus on evaluating the SAR at these positions. Although Marco and coworkers hypothesized the C4-ethyl group of pironetin was required for biological activity from their studies on the C4- and C5-positions of the α,β-unsaturated lactone in their simplified analogs **4.5**, their analogs were all found to be 1000-fold less active than pironetin in their antiproliferative assays. The significant

decreased activity of these simplified analogs could be due to the oversimplification of the pironetin structure. To explore the structure activity relationship at the C4- and C5-positions of pironetin, we sought to synthesize and evaluate pironetin analogs containing modification only at the C4- and C5-positions.

4.2 Synthesis of C4- and C-5 pironetin analogs. **4.2.1. Synthesis and evaluation of analogs lacking a C4-stereocenter**. To initially evaluate the SAR at the C4-position, we sought to determine if a substituent and/or a stereocenter is required at this position for biological activity. We thus sought to synthesize desethyl pironetin (**4.6a**) and the gem-dimethyl analog **4.6b**. In many of the previous total syntheses of pironetin, the stereoselective introduction of the ethyl group at the C4-position was more challenging than installing the methyl groups along the natural product's backbone. Methods for introducing the ethyl group in these total syntheses include the diastereoselective alkylation,[44,50] pentylation,[43] or aldol reactions[45-47,49] with reagent containing chiral auxiliaries. The ethyl group has also been introduced via a selective ring opening of a scalemic epoxide.[48,52,53,55] If the removal of the stereocenter at the C4-position is tolerated, this would significantly simplify the synthesis of future analogs.

Scheme 4-1. Retrosynthesis of desethyl and *gem*-dimethyl pironetin analogs



4.6a R = H
4.6b Me

4.7a R = H
4.7b Me

4.8a R = H
4.8b Me

4.9

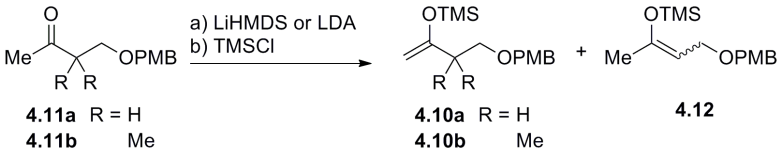
4.10a R = H
4.10b Me

4.2.1.1 Retrosynthesis. For the synthesis of analogs **4.6**, we chose to follow the synthetic route from Keck's pironetin total synthesis.[50] The lactone would be synthesized via methodology developed by Keck and coworkers for the synthesis of α,β-unsaturated lactones from β-acetoxy aldehydes **4.7** as shown in Scheme 4-1. This intermediate would be derived following functional group transformations of β-hydroxy ketones **4.8**. Intermediates **4.8** would be synthesized via the stereoselective Mukaiyama reaction between aldehyde **4.9** and silyl enol ethers **4.10**. The main difference between our route and Keck's reported route would be the silyl enol ether for the Mukaiyama aldol reaction. By following Keck's synthetic route, we could rapidly synthesize desired analogs **4.6** following previously reported conditions for the various transformations.

4.2.1.2 Forward synthesis. Since we previously synthesized aldehyde **4.9** for our previous SAR studies into the α-position of pironetin, we initially focused on the synthesis of silyl enol ethers **4.10**. The desired silyl enol ethers were synthesized following trapping of the lithium enolates of ketones **4.11** with TMSCl as shown in Scheme 4-2. The synthesis of silyl enol ether **4.10a** resulted in a mixture of products since ketone **4.11a** contained sterically accessible acidic protons at both α-positions of the ketone. Deprotonation of ketone **4.11a** with LDA and rapid quenching with TMSCl resulted in the synthesis of desired silyl enol ether **4.10a** along with silyl enol ether **4.12** as a 1.1:1 mixture. Byproduct **4.12** was generated due to deprotonation at the thermodynamically favored position of ketone **4.11a**. The silyl enol ethers were unstable to chromatography and used as a crude mixture without further purification. Since ketone **4.11b** only contained acidic protons at one α-position, the synthesis of silyl enol

ether **4.10b** proceeded without significant formation of additional byproducts. This silyl enol ether was also used without further purification.

Scheme 4-2. Synthesis of silyl enol ethers from ketones **4.11**



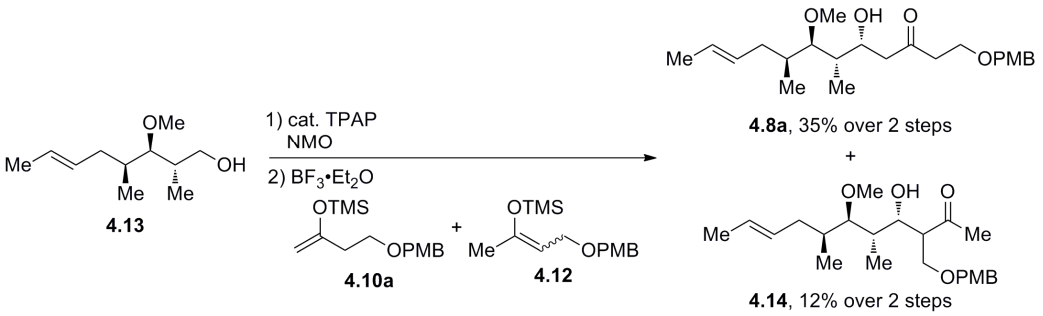
4.11a R = H
4.11b Me

4.10a R = H
4.10b Me

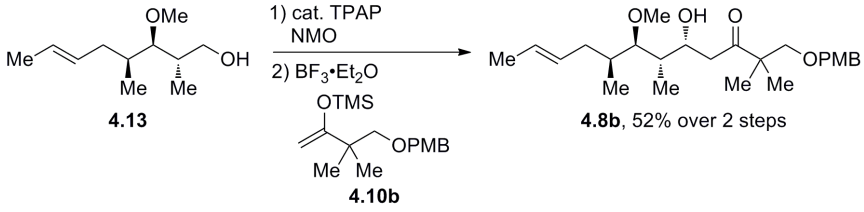
4.12

Following the synthesis of the required silyl enol ethers, we performed the desired stereoselective Mukaiyama aldol reaction with aldehyde **4.9** as shown in Schemes 4-3 and 4-4. The desired aldehyde was synthesized following oxidation of alcohol **4.13** which we previously synthesized during our syntheses of α-functionalized pironetin analogs. The aldehyde was reacted with silyl enols ethers **4.10** in the presence of BF_3•Et_2O to give β-hydroxy ketones **4.8** in moderate yield. The stereochemistry at the secondary alcohol was assigned based on models Evans and coworkers developed for the Mukaiyama reaction of aldehydes containing an α-substituent and/or a β-alkoxy substituent.[62] For the reaction between silyl enol ethers **4.10a** and **4.12** with aldehyde **4.9**, the desired product **4.8a** was synthesized along with byproduct **4.14** resulting from the Mukaiyama aldol with silyl enol ether **4.12**. Even though the reaction was performed with near statistical mixture of silyl enol ethers, we hypothesized β-hydroxy ketone **4.8a** was the major product due to faster rate of addition of silyl enol **4.10a** over **4.12** to the aldehyde.

Scheme 4-3. Seteroselective Mukaiyama aldol wih silyl enol ethers **4.10a** and **4.12**

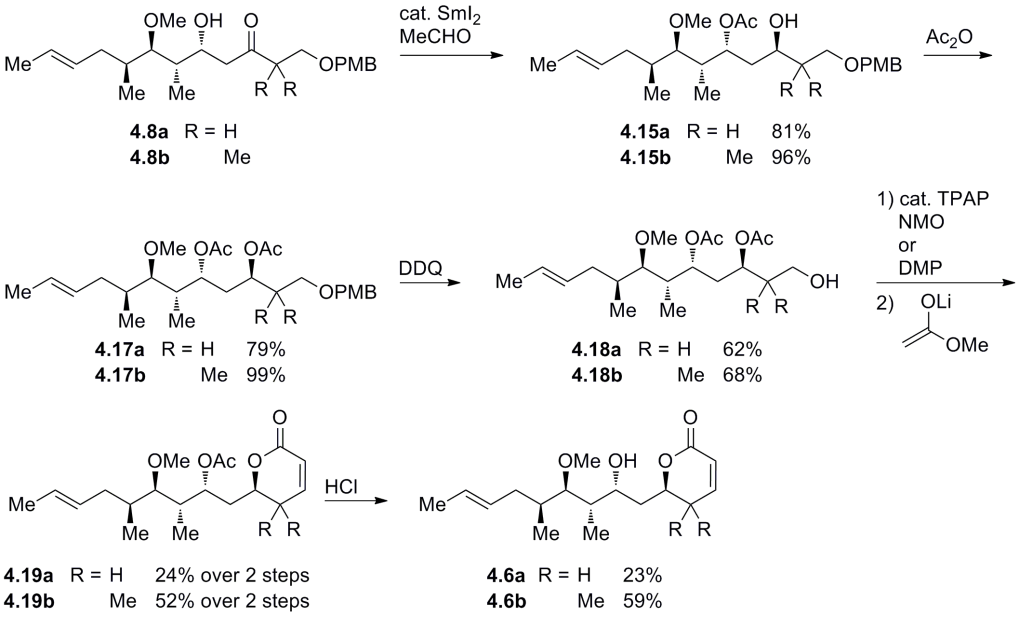


Scheme 4-4. Seteroselective Mukaiyama aldol with silyl enol ether **4.10b**



From intermediates **4.8**, we continued the synthesis of the desired analogs **4.6** following a similar synthetic route reported by Keck and coworkers as shown in Scheme 4-5. A SmI_2-catalyzed *anti*-selective disproportionation[63] between β-hydroxy ketone **4.8** and acetaldehyde resulted in the formation of the desired intermediates **4.15**. The relative geometries of the secondary alcohols of intermediates **4.15** were assigned following hydrolysis of the acetate esters and conversion of the resulting diol to the corresponding acetonides **4.16** as shown in Scheme 4-6. The ^{13}C NMR resonances of the acetonide carbons in acetonides **4.16** (Figures 4-3 and 4-4) were consistent with the chemical shifts of the *anti*-1,3-diol acetonide.[64]

Scheme 4-5. Synthesis of analogs **4.6**



4.8a R = H
4.8b Me

4.15a R = H 81%
4.15b Me 96%

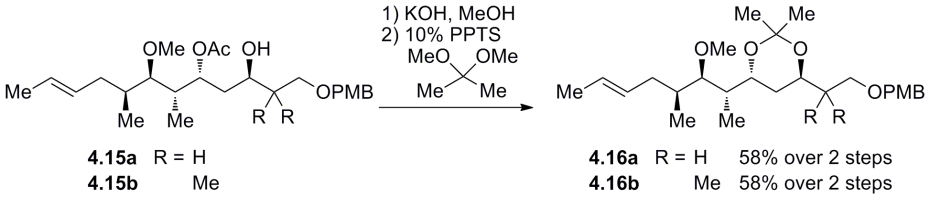
4.17a R = H 79%
4.17b Me 99%

4.18a R = H 62%
4.18b Me 68%

4.19a R = H 24% over 2 steps
4.19b Me 52% over 2 steps

4.6a R = H 23%
4.6b Me 59%

Scheme 4-6. Synthesis of acetonides **4.16** for ^{13}C NMR analysis



4.15a R = H
4.15b Me

4.16a R = H 58% over 2 steps
4.16b Me 58% over 2 steps

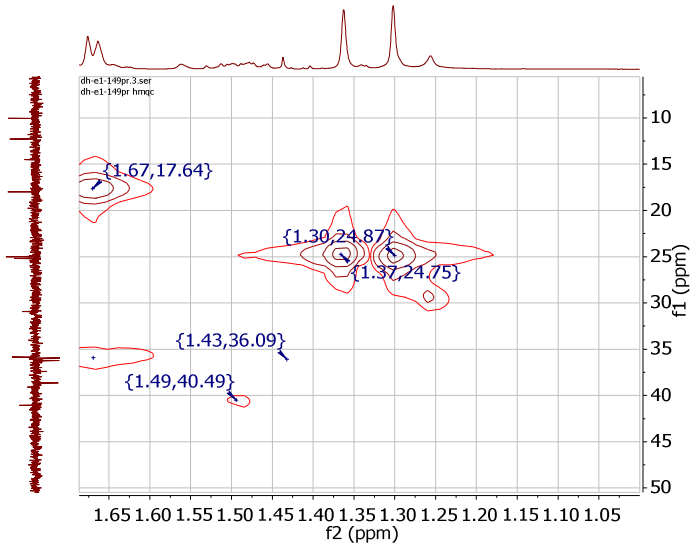


Figure 4-3. HMQC crosspeaks of acetonide **4.16a**.

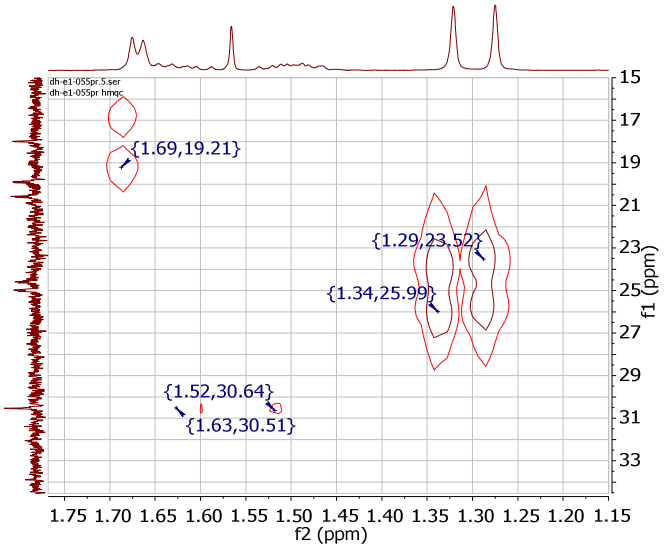


Figure 4-4. HMQC crosspeaks of acetonide **4.16b**.

Intermediate **4.15** was converted to primary alcohol **4.18** following protection of the secondary alcohol as the acetate ester and removal of the PMB protecting group. The primary alcohol was oxidized to desired aldehydes **4.7** and reacted with the lithium enolate of methyl acetate to yield α,β-unsaturated lactones **4.19**. The acetate group was hydrolyzed under acidic conditions to yield the desired desethyl and *gem*-dimethyl pironetin analogs **4.6a** and **4.6b** respectively.

4.2.1.3 Biological activity. The antiproliferative activity of analogs **4.6** was evaluated against drug-sensitive OVCAR5 and A2780 ovarian cancer cell lines and a cisplatin-resistant A2780-CP cell line. Analogs **4.6a** and **4.6b** were found to be inactive with GI_{50} values >10 μM and >100 μM respectively. These results reveals that the C4-ethyl group cannot be replaced by a hydrogen or a *gem*-dimethyl moiety.

4.2.2 Synthesis and evaluation of the analogs with varying stereochemistry at the C4-, and C5-positions. To further explore the structure activity relationship of the α,β-

unsaturated pironetin lactone, we sought to synthesize analogs **4.20**-**4.22** (Figure 4-5), which are C4- and/or C5-stereoisomers of pironetin.

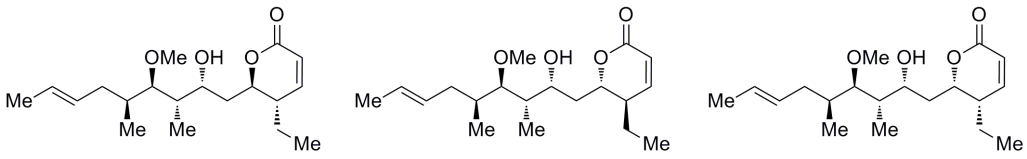
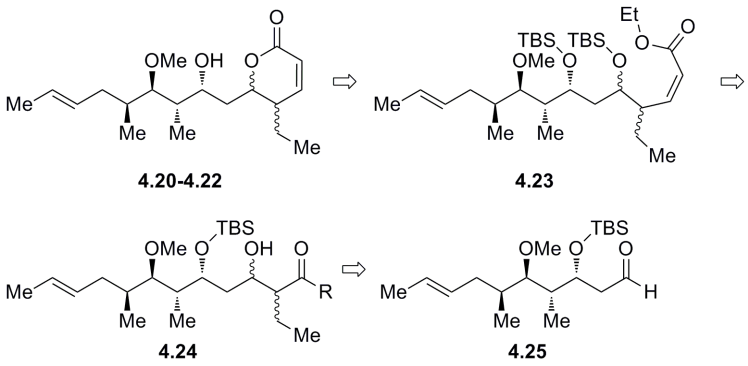


Figure 4-5. Pironetin analogs containing different stereochemistry at the C4- and C5-positions.

4.2.2.1 Retrosynthesis. For the synthesis of our desired analogs, we proposed the α,β-unsaturated lactones would be synthesized via lactonization of intermediate **4.23**, which results from a Z-selective olefination of aldehyde **4.24** as shown in Scheme 4-7. This synthetic strategy has been utilized by multiple groups for the synthesis of the α,β-unsaturated lactone of pironetin.[44-46,48,49,52,53] We previously utilized this strategy for the synthesis of our α-functionalized pironetin analogs. We proposed the desired stereochemistry at the C4- and C5-positions of our analogs could be established via the appropriate *syn*- or *anti*-aldol reaction with aldehyde **4.25**. We previously synthesized aldehyde **4.25** during our studies into the SAR of the α-position of pironetin.

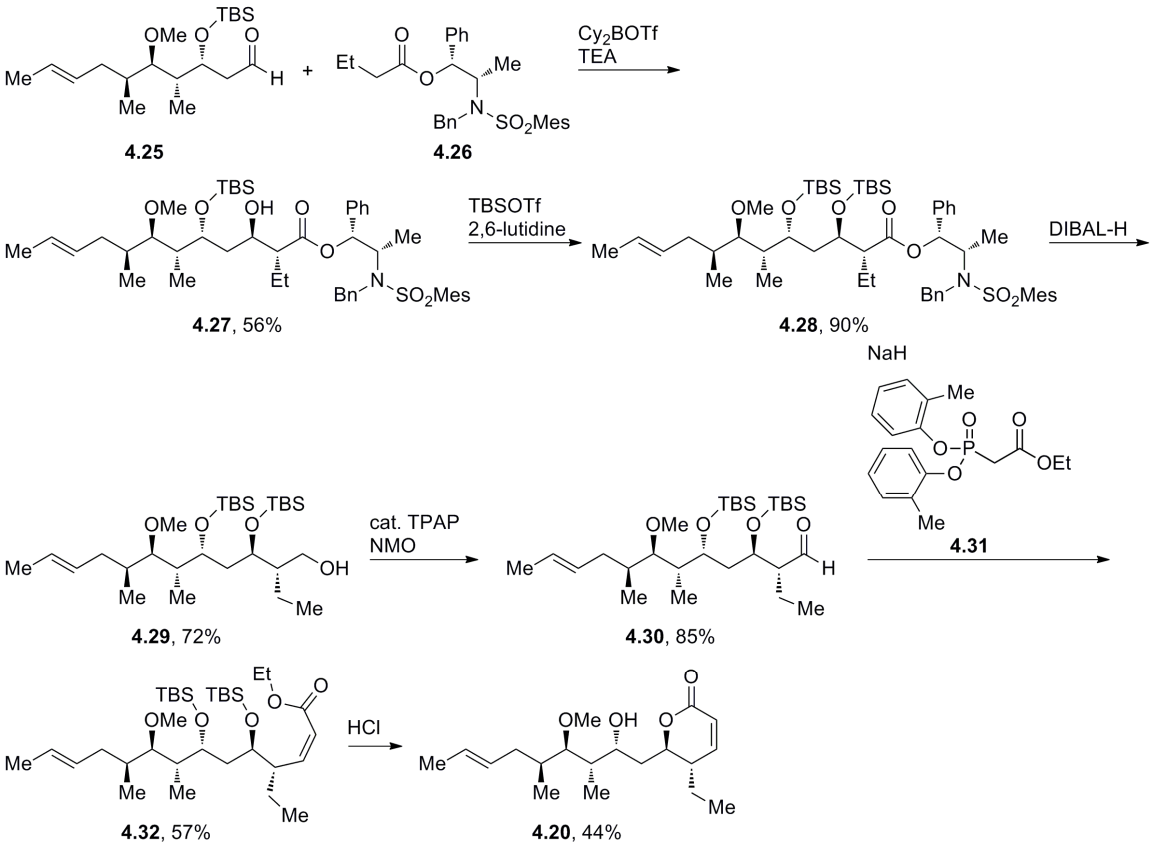
Scheme 4-7. Retrosynthesis of analogs **4.20**-**4.22** from aldehyde **4.25**



4.2.2.2 Synthesis of C4-*epi* and C5-*epi* pironetin analogs. For the synthesis of the C4-*epi*-pironetin analog **4.20**, the relative configuration between the C4- and C5- positions

requires an *anti*-selective aldol with aldehyde **4.25**. Evans and coworkers have reported the *anti*-selective aldol between thiazolidinethiones and conjugated aldehydes or benzaldehydes.[99] The *anti*-selective thiazolidinethione aldol reaction with aldehyde **4.25** under these previously reported reaction conditions were unsuccessful. The *anti*-selective reactions have been reported with norephedrine esters developed by Masamune and coworkers.[100]

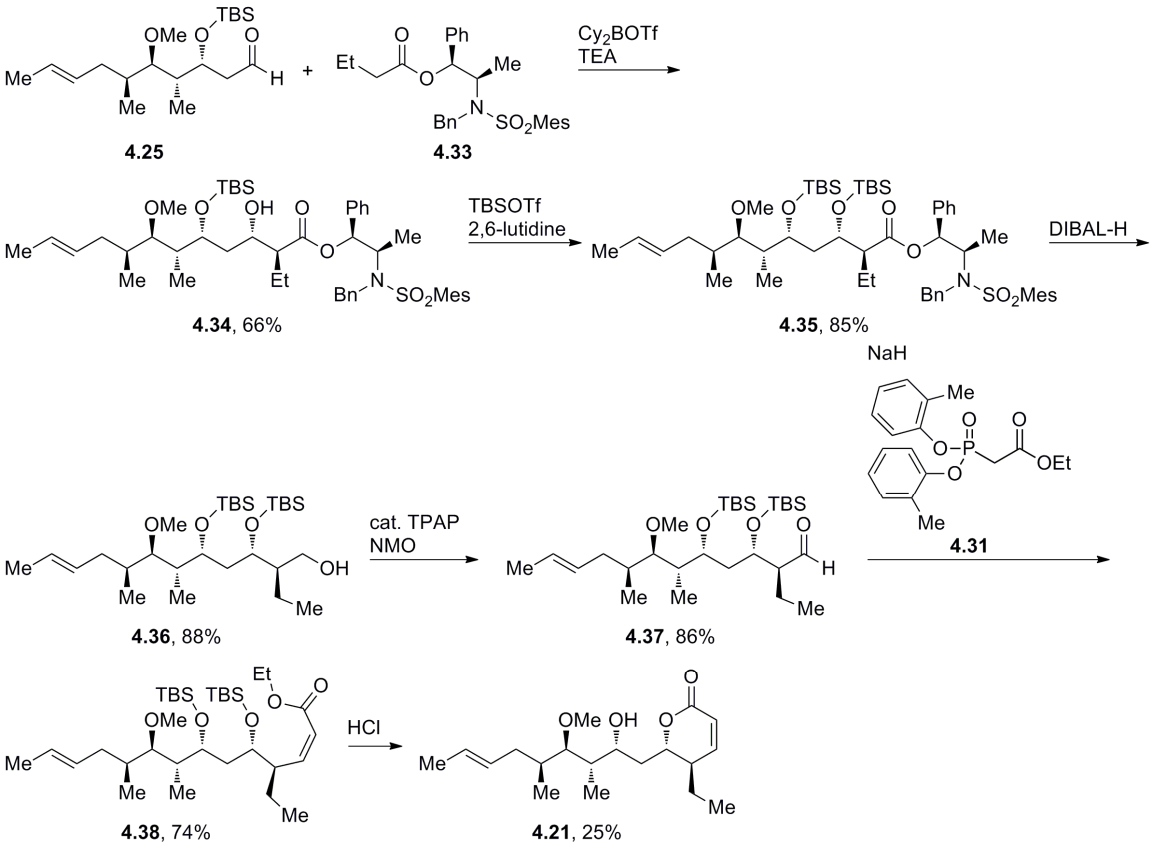
Scheme 4-8. Synthesis of C4-*epi*-pironetin **4.20**



Aldehyde **4.25** was reacted with the boron enolate of norephedrine ester **4.26** to give β-hydroxy ester **4.27** as shown in Scheme 4-8. Subsequent protection of the secondary alcohol as the TBS ether and diisobutylaluminum aluminum hydride reduction of the ester resulted in intermediate **4.29**. The primary alcohol was oxidized to the aldehyde

4.30 and carried forward to intermediate **4.32** following the *Z*-selective olefin with Ando type phosphonate **4.31**. We completed the synthesis of our desired analog **4.20** via a one-pot lactonization and TBS-deprotection of ester **4.32** for the synthesis of the α,β-unsaturated lactone. The C5-*epi*-pironetin analog **4.21** was synthesized following the same route but with the *anti*-selective aldol reaction being performed with ester **4.33** as shown in Scheme 4-9.

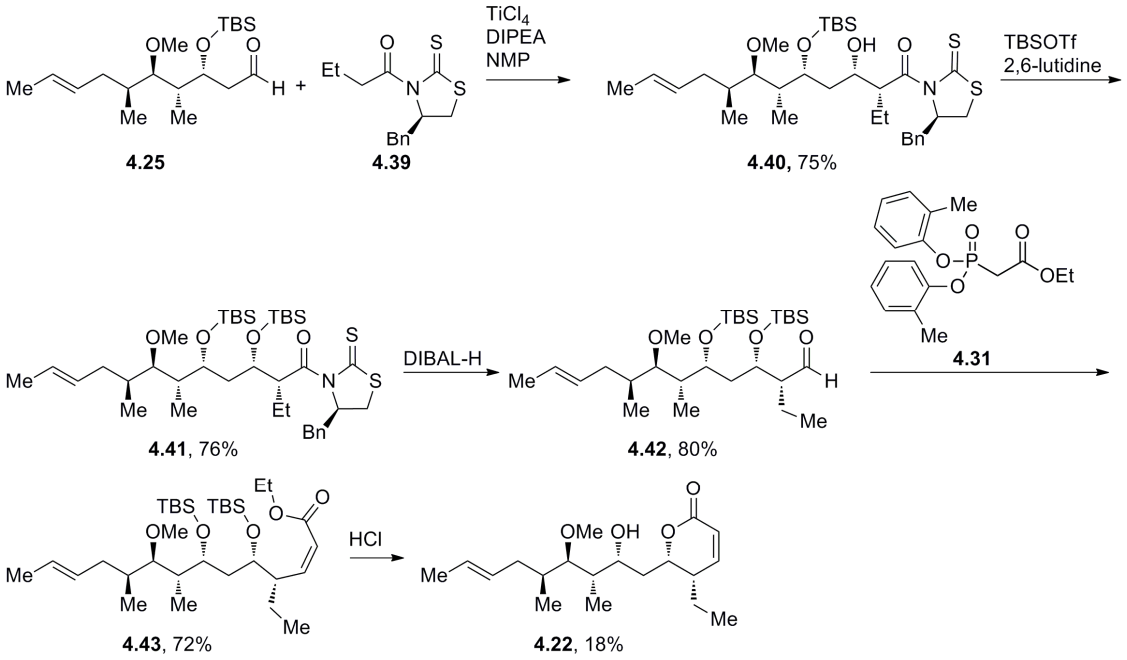
Scheme 4-9. Synthesis of C5-*epi*-pironetin **4.21**



4.2.2.3 Synthesis of C4-, C5-*epi* pironetin analog. Since the C4, C5-*epi*-pironetin analog **4.22** contains a *syn*-relationship between the C4- and C5- positions, thiazolidinethione based *syn*-aldol methodologies could be applied for the synthesis of the desired analog.[101] Aldol reaction between aldehyde **4.25** and thiazolidinethione **4.39**

established the desired stereochemistry at the C4- and C5- positions as shown in Scheme 4-10. Following protection of the secondary alcohol in intermediate **4.40** as the TBS ether, thiazolidinethione **4.41** was converted to aldehyde **4.42** following DIBAL-H cleavage of the chiral auxiliary. The synthesis of analog **4.22** was completed from aldehyde **4.42** via previously utilized *Z*-olefination and lactonization methodology for the synthesis of the α,β-unsaturated lactone.

Scheme 4-10. Synthesis of C4,C5-*epi*-pironetin **4.22**

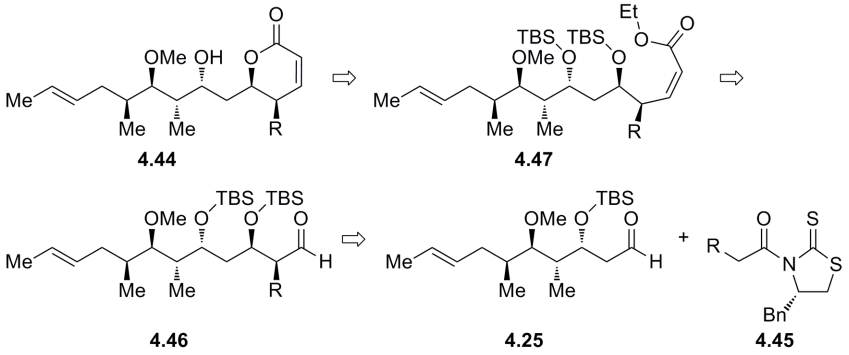


4.2.2.4. Biological activity. The antiproliferative activity of analogs **4.20**-**4.22** were evaluated against drug-sensitive OCVAR5 and A2780 ovarian cancer cell lines and a cisplatin-resistant A2780-CP cell line. These analogs were also found to be inactive with GI_{50} values >30 μM. These results suggest modifying either the stereochemistry at either the C4- and C5-position results in loss of biological activity.

4.2.3 Synthesis of C4-pironetin analogs. Since our initial SAR into the C4- and C5-positions of pironetin suggests a group at the C4-position with the same absolute stereochemistry as the natural product is required for biological activity, we proposed to synthesize additional pironetin analogs **4.44** containing different substituents at C4-position to further evaluate the SAR at the this position.

4.2.3.1 Retrosynthesis. For the synthesis of our desired analogs, we propose to synthesize our analogs following the synthetic route used for the synthesis of C4-,C5-*epi*-pironetin analog **4.22** as shown in Scheme 4-11. The α,β-unsaturated lactone would be synthesized following the previously utilized olefination/lactonization strategy from aldehyde **4.46**. We proposed to introduce different functional groups at the C4-position via a diastereoselective aldol reaction between aldehyde **4.25** and thiazolidinethione **4.45** containing various groups.

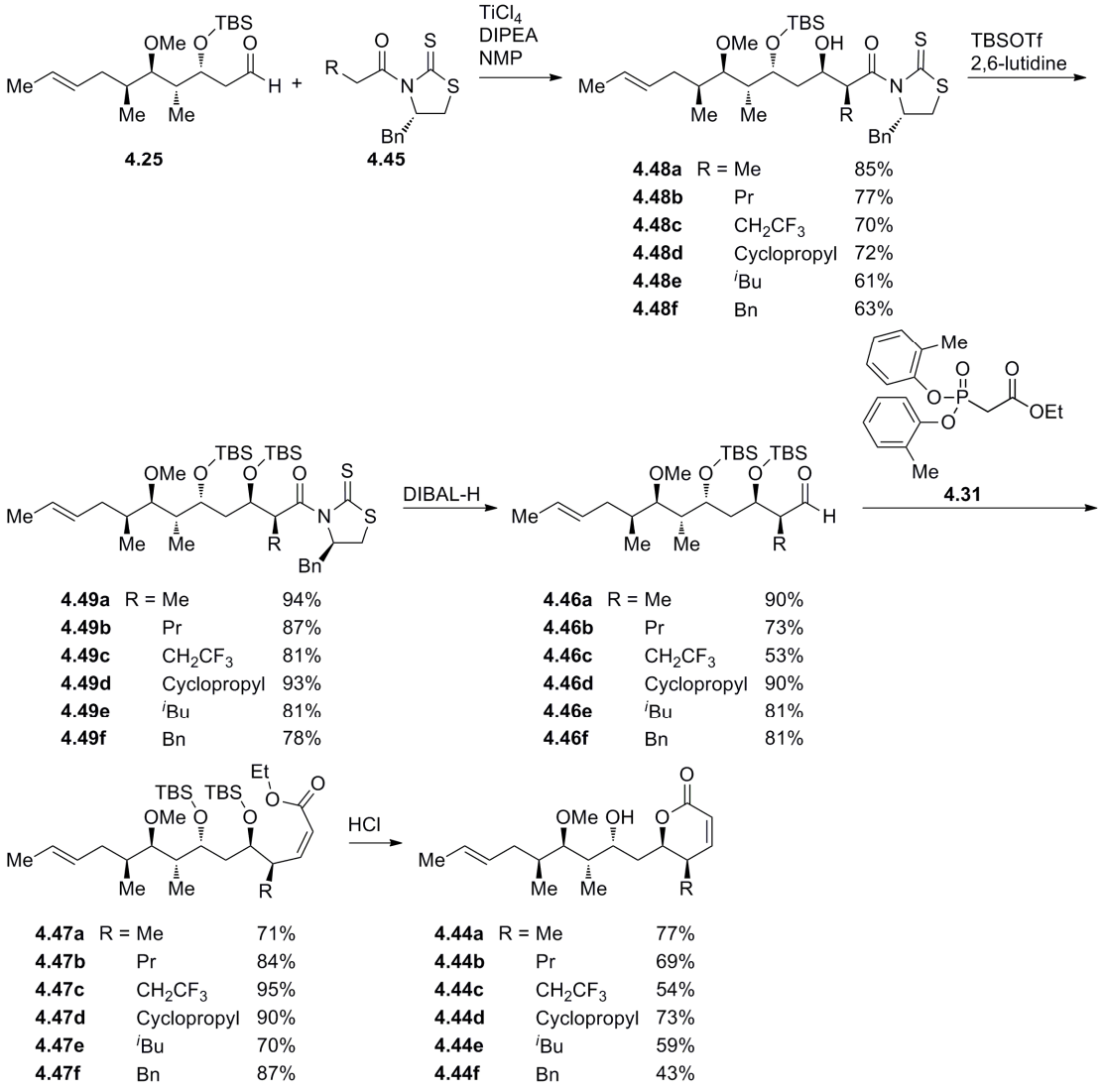
Scheme 4-11. Retrosynthesis of analogs **4.44** containing different groups at the C4-position



4.2.3.2 Forward synthesis general route. Similar to our synthesis of analog **4.22**, groups at the C4-position were introduced with the correct stereochemistry following *syn*-aldol addition of the titanium enolate of thiazolidinethiones **4.45** into aldehyde **4.25** as shown in Scheme 4-12. We focused on only introducing hydrophobic groups at this position to evaluate the effect of groups with different steric properties. We successfully

performed the diastereoselective aldol reaction with thiazolidinethione **4.45** containing groups such as the linear and branched alkyl groups, and also a cyclopropyl group. We completed the synthesis of analogs **4.44** from intermediates aldehyde **4.48** following the same synthetic routes utilized for the synthesis of C4-, C5-*epi* pironetin analog **4.22**.

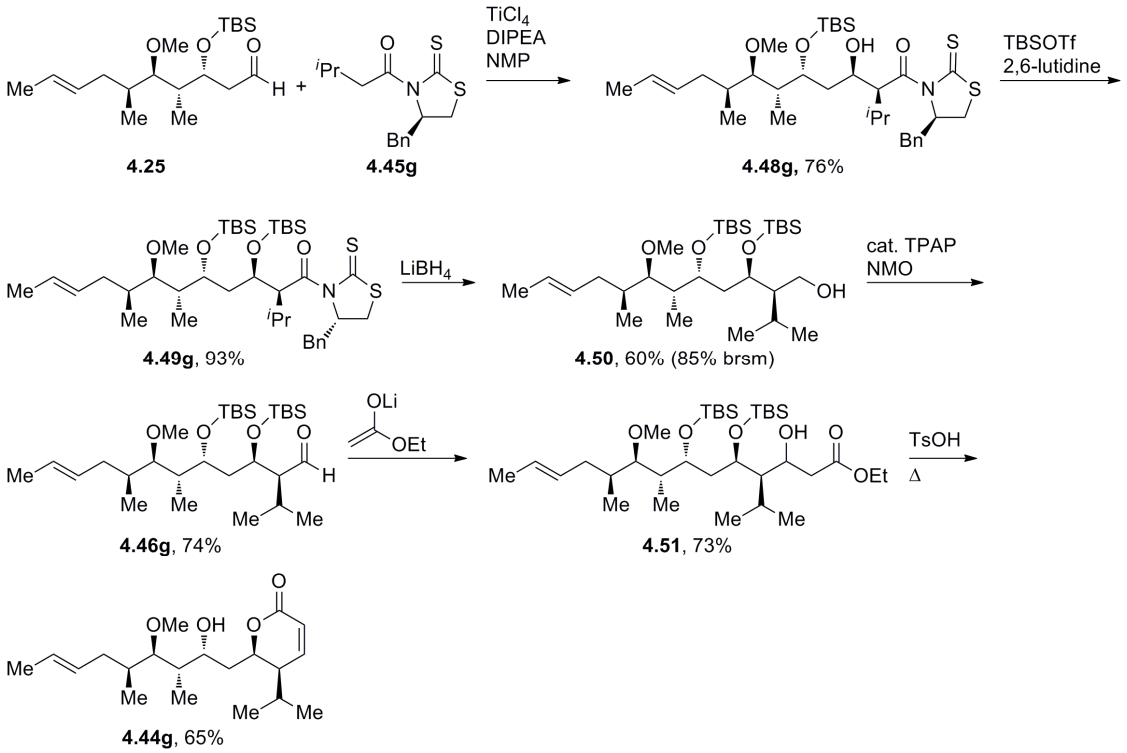
Scheme 4-12. Synthesis of analogs **4.44** containing different groups at the C4-position



4.2.3.3 Synthesis of the isopropyl pironetin analog. While we completed the syntheses of analogs containing a branched substituents at the C4-position such as the cyclopropyl and the isobutyl group, the synthesis of the isopropyl analog **4.44g** required different

methodologies for the synthesis of the α,β-unsaturated lactone. We successfully introduced the isopropyl group following the aldol reaction and the between aldehyde **4.25** and thiazolidinethione **4.45g** as shown in Scheme 4-13.

Scheme 4-13. Synthesis of isopropyl pironetin analog **4.44g**

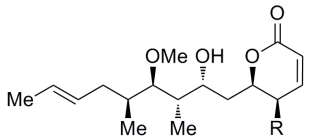


The diisobutylaluminum hydride reduction of intermediate **4.49g**, however, resulted in aldehyde **4.46g** in only 8% yield along with alcohol **4.50** in 21% yield and 62% recovered starting material. We hypothesized that the steric properties of the isopropyl group hindered the diisobutylaluminum hydride cleavage of the chiral auxiliary. Due to the mixture of products from the diisobutylaluminum hydride reduction, we chose to cleave the chiral auxiliary of intermediate **4.49g** with a less sterically-bulky reagent. The reduction of sterically-hindered oxazolidineone amides and thiazolidineone amides to the corresponding aldehyde has been reported with lithium borohydride.[102-104] The lithium

borohydride reduction of amide **4.49g** resulted in alcohol **4.50** in moderate yield. The primary alcohol was subsequently oxidized to the desired aldehyde **4.46g**. Our previous strategy for synthesizing the α,β-unsaturated lactone via a *Z*-selective olefination and lactonization reactions were unsuitable for the synthesis of the isopropyl analog. The reaction between phosphonate ester **4.31** and aldehyde **4.46g** did not occur even in the presence of 10 equivalents of the phosphonate ester. The steric properties of the isopropyl group could also hinder the addition of the phosphonate ester into the aldehyde. Thus, we sought an alternative method for the synthesis of the α,β-unsaturated lactone involving less sterically demanding reagents. Nelson and coworkers previously reported the synthesis of the pironetin α,β-unsaturated lactone via a one pot ester hydrolysis, lactonization, and subsequent β-hydroxyl group elimination of a β,δ ester diol.[51] Following a similar strategy for the synthesis of the isopropyl analog, the acetate aldol between aldehyde **4.46g** and the lithium enolate of ethyl acetate resulted in β-hydroxy ester **4.51**. Heating intermediate **4.51** in the presence of toluenesulfonic acid afforded a one pot silyl ether deprotection, ester hydrolysis, lactonization and elimination resulting in desired analog **4.44g**. The α,β-unsaturated lactone was synthesized from aldehyde **4.46g** in comparable yield through this alternative route as our general olefination/lactonization route.

4.2.3.4. Biological Activity. The antiproliferative activities of analogs **4.44** were evaluated in our previously used panel of ovarian cancer cell lines; the measured GI_{50} values are shown in Table 4-1.

Table 4-1. Antiproliferative activity of C4-pironetin analogs **4.44**



4.44

Entry	Compound	R	GI_{50} (nM)[a] OVCAR5[b]	A2780[b]	A2780-CP[c]
1	Paclitaxel	-	38.8 ± 2.7	19.6 ± 4.9	41.5 ± 3.5
2	Pironetin (**4.1**)	Et	21.9 ± 2.5	41.0 ± 1.5	23.5 ± 1.3
3	**4.44a**	Me	183 ± 24	138 ± 20	88.2 ± 4.8
4	**4.44b**	Pr	64.9 ± 9.2	89.1 ± 3.3	71.4 ± 3.6
5	**4.44c**	CH_2CF_3	371 ± 53	280 ± 21	296 ± 22
6	**4.44d**	Cyclopropyl	53.1 ± 9.2	66.2 ± 6.2	50.0 ± 1.9
7	**4.44e**	^{i}Bu	183 ± 12	239 ± 11	176 ± 6
8	**4.44f**	Bn	>10,000	>10,000	>10,000
9	**4.44g**	^{i}Pr	2,050 ± 330	3,270 ± 360	2,730 ± 110

[a] Average of 2 experiments performed in triplicate ± SEM (n = 6)
[b] Drug-sensitive ovarian cancer cell line
[c] Cisplatin-resistant ovarian cancer cell line

In our assay, pironetin (Table 4-1, entry 2) had comparable activity to paclitaxel (Table 4-1, entry 1) across our panel of ovarian cancer cell lines. We found limited substitution is also tolerated at the C4-position, smaller group such as the methyl group (Table 4-1, entry 3) or larger groups such as the isobutyl (Table 4-1, entry 7) and benzyl (Table 4-1, entry 8) group at this position resulted in decreased biological activity. While a propyl (Table 4-1, entry 4) and cyclopropyl (Table 4-1, entry 6) containing analogs have comparable activity to pironetin, the isopropyl analog **4.44g** (Table 4-1, entry 9) showed a 100-fold decrease in biological activity compared to the natural product.

4.3 Molecular modeling of synthesized pironetin analogs. After we completed the syntheses and evaluation of the biological activity of our various C4- and/or C5-pironetin analogs, the crystal structures of pironetin bound to α-tubulin in an α-tubulin/β-tubulin/statmin-4/tubulin tyrosine ligase complex were reported by multiple groups.[36,37] Pironetin was shown to bind in an induced binding site in α-tubulin with the C4-ethyl

group of the natural product occupying a hydrophobic pocket in the binding site (Figure 4-6). This size of the hydrophobic pocket occupied by the C4-ethyl group of pironetin could be cause for the limited steric properties of groups tolerated at the C4-position of our pironetin analogs.

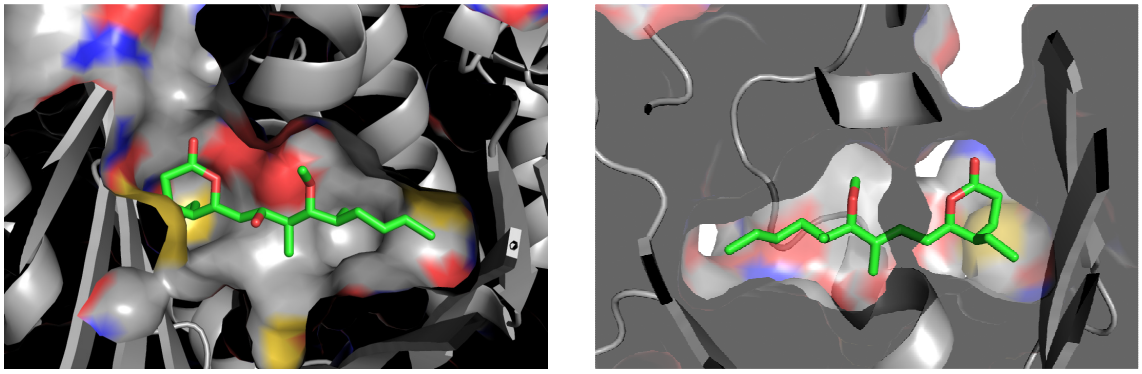
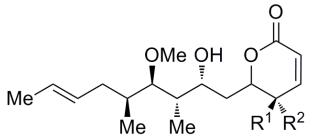


Figure 4-6. X-ray crystal structure of pironetin bound to α-tubulin (PDB ID 5FNV).

Since our analogs had a range of antiproliferative activity, we sought to determine if molecular modeling could be used as a tool for the design of future analogs. Analogs **4.6**, **4.20-4.22** and **4.44** were docked into the identified pironetin binding site in α-tubulin.[36,37] Since pironetin is a covalent inhibitor, docking scores were calculated using CovDock module in the Schrödinger® Maestro software package;[105] the CovDock module provides docking score, glide score and covdock affinity for each ligand pose. We were interested if either of these values correlated with the measured biological activity; the best docking score, glide score and covdock affinity from multiple poses of each analog were compared to the antiproliferative activity in OVCAR5 ovarian cancer cell line as shown in Table 4-2. A correlation was not observed between either of the CovDock scores and the observed biological activity. Although molecular modeling is a

useful tool for drug discovery, computer-based drug design may have limited application for the design of pironetin analogs.

Table 4-2. Comparison of OVCAR5 antiproliferative activities with CovDock scores



Entry	Compound	R^1	R^2	C5-Geometry	OVCAR5 GI_{50} (nM)[a,b]	Cdock Affinity[c]	Docking Score[c]	Glide Score[c]
1	Pironetin (**4.1**)	Et	H	*R*	21.9 ± 2.5	-7.788	-7.323	-8.422
2	**4.44d**	Cyclopropyl	H	*R*	53.1 ± 9.2	-7.782	-7.327	-8.431
3	**4.44b**	Pr	H	*R*	64.9 ± 9.2	-7.267	-7.287	-8.158
4	**4.44a**	Me	H	*R*	183 ± 24	-7.214	-6.734	-7.540
5	**4.44e**	^{i}Bu	H	*R*	183 ± 12	-7.826	-7.728	-8.319
6	**4.44c**	CH_2CF_3	H	*R*	371 ± 53	-8.755	-8.334	-9.176
7	**4.44g**	^{i}Pr	H	*R*	2,050 ± 330	-7.325	-7.152	-8.018
8	**4.44f**	Bn	H	*R*	>10,000	-9.055	-8.851	-9.576
9	**4.6a**	H	H	*S*[d]	>10,000	-6.377	-5.609	-7.257
10	**4.6b**	Me	Me	*R*	>100,000	-7.156	-6.882	-7.677
11	**4.20**	H	Et	*R*	>30,000	-7.554	-7.247	-7.862
12	**4.21**	Et	H	*S*	>30,000	-7.611	-7.168	-8.091
13	**4.22**	H	Et	*S*	>30,000	-7.478	-7.407	-7.588

[a] Average of 2 experiments performs in triplicate ± SEM (n = 6)
[b] Drug-sensitive ovarian cancer cell line
[c] Highest score from 10 docking poses of the ligand
[d] Cahn-Ingold-Prelog assignment of C5-stereocenter effected by lack of lack of a C4-substituent

4.4 Conclusion. We have synthesized a series of pironetin analogs containing modification only at the C4- and C5- position of the α,β-unsaturated lactone and evaluated their antiproliferative activity. By modifying only these positions, we systematically evaluated the structure-activity relationship at these positions of pironetin. Since analogs **4.44** containing either a propyl or cyclopropyl group at the C4-position were shown to have comparable antiproliferative activity to pironetin with nanomolar GI_{50} values, the binding pocket may not be able to accommodate larger groups at this position. We have also found that modifying the stereochemistry at either of these positions results in the loss of biological activity. These results suggest that the confirmation of the α,β-unsaturated lactone is important for biological activity Unlike

previous studies by Marco and coworkers with simplified analogs **4.5** (Figure 4-2),[28,74] we found that modification of the C5-stereocenter in pironetin also results in a loss of biological activity. From our SAR studies, we have shown that a single substitution at the C4-position of pironetin with the same stereochemistry of the α,β-unsaturated lactone as the natural product is required for biological activity.

CHAPTER 5. SYNTHESIS AND EVALUATION OF ANALOGS TO IMPROVE PIRONETIN'S METABOLIC STABILITY

5.1 Introduction. While pironetin (**5.1**) has potent *in vitro* activity against a variety of cancer cell lines, the natural product was found to have poor efficacy *in vivo* in mice bearing P388 murine leukemia cells.[33] We hypothesized that the poor *in vivo* activity could be due to pironetin's poor metabolic stability. In our initial evaluation of pironetin's PK/PD properties, the natural product was found to be rapidly metabolized in human and mouse liver microsomes. To improve pironetin's *in vivo* activity, we sought to synthesize analogs with improved metabolic stability.

5.2 Evaluation of pironetin's metabolism and potential metabolites. In order to design pironetin analogs with increased metabolic stability, we needed to identify the natural product's sites of metabolism.

5.2.1 Predicted sites of metabolism. Due to the instrumentation required for metabolite identification studies, we initially predicted the sites of metabolism using the SMARTCyp program. SMARTCyp is a online tool developed by researchers at the University of Copenhagen to predict sites of cytochrome P450 metabolism.[106-110] Cytochrome P450s are enzymes containing a heme iron which oxidize substrates using molecular oxygen.[111] The software predicts sites which undergo metabolism by the various isoforms of cytochrome P450 along with sites specific for metabolism via CYP2C and CYP2D6 isoforms; the top predicted sites of metabolism are shown in Figure 5-1.

Figure 5-1. SMARTCyp predicted sites of metbolism of pironetin.

The models predicted sites of metabolism on the α,β-unsaturated lactone of pironetin. The model predicting sites of metabolism for the various P450 isoforms also predicted the methyl ether to undergo P450 metabolism. Predicted sites of metabolism specific for the CYP2C and CYP2D6 isoforms include the non-conjugated olefin and neighboring allylic positions.

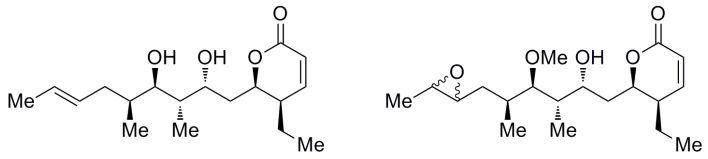


Figure 5-2. Structure of potential pironetin metabolites.

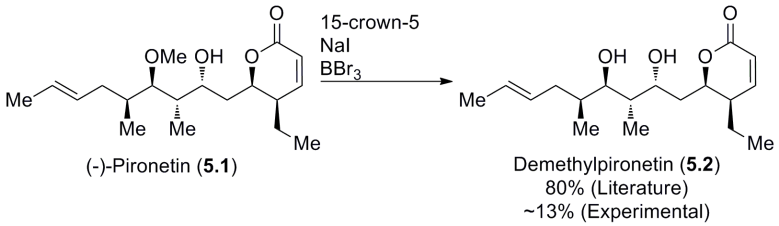
5.2.2 Previous studies on predicted metabolites. Based on these predicted sites of metabolism, we hypothesized the structure of the potential metabolites. Two potential metabolites are demethylpironetin/NK10958P (**5.2**) and epoxypironetin (**5.3**) (Figure 5-2). Demethylpironetin could result from demethylation of pironetin via P450 oxidation of the methyl ether to the formaldyde hemiacetal and subsequent elimination of acetaldehyde. Epoxypironetin would result from P450 oxidation of the non-conjugated olefin. We focused on these two potential metabolites since the biological activity of both compounds had previously been reported in the literature.

Demethylpironetin/NK10958P (**5.2**) is a natural product previously isolated from a fermentation of a pironetin-producing *Streptomyces* strain.[112] The demethyl analog **5.2**

was previously found to have comparable activity as pironetin in tubulin disassembly assays and cell cycle arrest assays.[33,34] Epoxypironetin (**5.3**) was reported to be less active than the natural product.[33,34] In assays measuring cell cycle arrest, the percentage of the cell population arrested in the G2/M-phase in cells treated with 500 ng/mL of epoxide **5.3** were similar to cells treated with 50 and 100 ng/mL of pironetin.. Epoxypironetin was also reported to disrupt tubulin polymerization at 50-fold greater concentrations than the natural product.

5.2.3 Synthesis and evaluation of demethylpironetin. Since demethylpironetin is a potential bioactive metabolite, we were interested in obtaining demethyl analog **5.2** as a standard for future metabolite identification studies. Kitahara and coworkers previously reported the semi-synthesis of demethylpironetin in 80% yield following the demethylation of pironetin.[52] We attempted to repeat the synthesis of demethylpironetin following previously reported conditions; the reaction resulted in a mixture of products and we only obtained desired product in 13% as shown in Scheme 5-1.

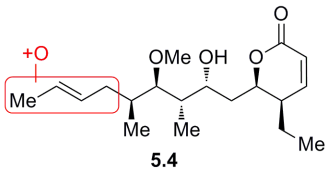
Scheme 5-1. Demethylation of pironetin



Although the analog **5.2** was obtained in low yield, we obtained sufficient amount of material to evaluate its antiproliferative activity which had not been previously been reported in the literature. We evaluated its antiproliferative activity against drug sensitive OVCAR5 cell line; demethylpironetin (**5.2**) was found to have comparable activity to

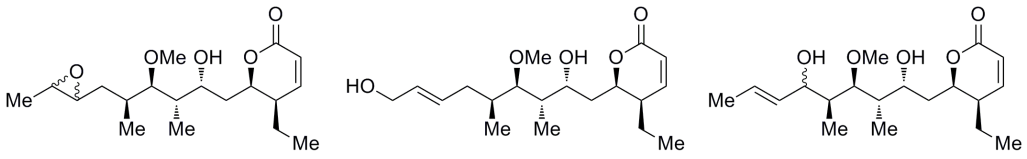
pironetin with a GI_{50} value of 64.2 ± 2.9 nM compared to GI_{50} value of 21.5 ± 0.7 nM for pironetin.

5.2.4 Identification of the sites of metabolism. Although we predicted the sites of metabolism of pironetin through the SMARTCyp program, we chose to experimentally identify the sites of metabolism of pironetin; metabolite identification studies were performed with human liver microsomes as an *in vitro* method to identify potential human metabolites. Sara Coulup in our group collaborated with Dr. Natalia Tretyakova for initial metabolite identification studies. LC-MS/MS analysis of aliquots taken from the incubation of pironetin in human liver microsomes showed the primary metabolite **5.4** to result from oxidation at a position around the non-conjugated olefin as shown in Figure 5-3. We hypothesized the structure of metabolite **5.4** could be epoxypironetin (**5.3**) or allylic alcohols **5.5** and **5.6** (Figure 5-4); the MS/MS fragmentation pattern of metabolite **5.4** matched that of epoxide **5.3** independently synthesized in our group. We have not excluded alcohols **5.5** and **5.6** as the primary metabolite due to the difficulty of synthesizing these analogs via semi-synthesis. The demethylpironetin **5.2** was only observed in trace amounts during these studies.



5.4

Figure 5-3. Primary metabolite from initial metabolite identificaiton assay in human liver microsomes.



Epoxypironetin (**5.3**) **5.5** **5.6**

Figure 5-4. Potential structures of primary metabolite **5.4**.

We also submitted pironetin to Pharmaron, a CRO, for similar metabolite identification studies form human liver microsomes. In these parallel studies, 14 metabolites of pironetin were identified over a 15 min incubation of pironetin in human liver microsomes. These studies also suggest the primary initial site of metabolism to be the non-conjugated olefin. A number of the metabolites identified by Pharmaron were proposed to result from further oxidation of metabolite **5.4**; the general structure of these metabolites is shown in Figure 5-5. Demethylpironetin **5.2** was also not detected in the assay performed by Pharmaron. Demethylation of the methyl ether of pironetin was only observed in metabolites **5.9** and **5.10** which had undergone oxidation at other positions of the natural product.

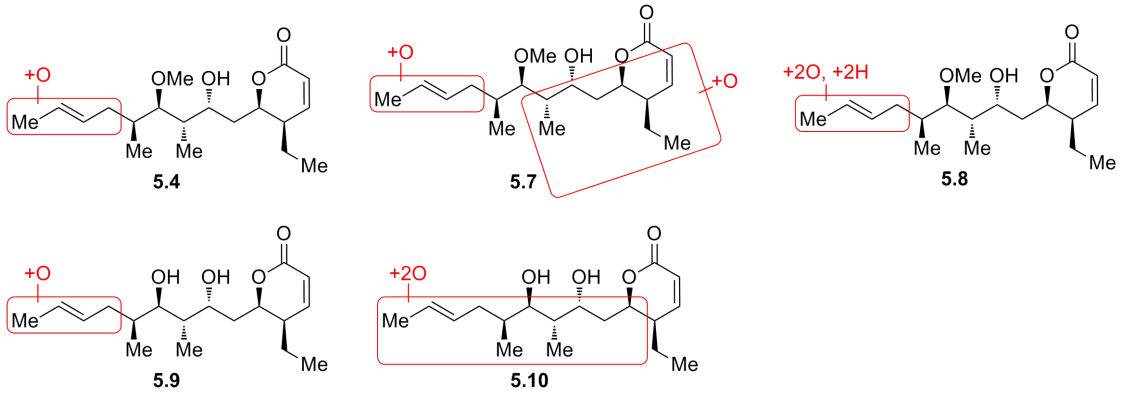
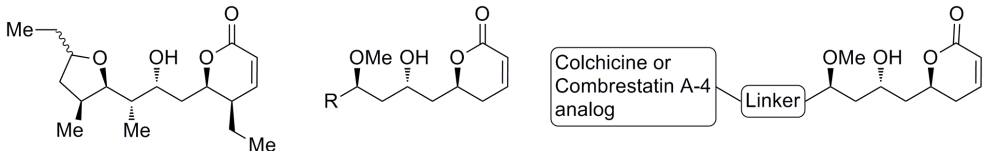


Figure 5-5. Strucutre of pironetin human liver microsome metabolites identified by Pharmaron.

5.3 Synthesis and evaluation of phenylpironetin. Since the primary site of metabolism identified from both metabolite identification studies was the non-conjugated olefin, we sought the replace this group with one which would be less prone to undergo metabolism.

5.3.1 Previous SAR on the non-conjugated olefin. In addition to epoxypironetin (**5.3**), a limited number of pironetin analogs containing modifications at the non-conjugated olefin have been reported in the literature (Figure 5-6). Analog **5.11** was synthesized by

Kitahara and coworkers following TMSI-promoted demethylation and cyclization of pironetin; this analog was found to be 1,000 fold less active than the pironetin in microtubule disassembly assays.[97] Marco and coworkers have synthesized simplified analogs **5.12** containing either long alkyl chains or a phenyl group instead of a non-conjugated olefin; these analogs were found to be 10,000-fold less active than pironetin in antiproliferative assays.[28,113] More recently, the same group has synthesized a series of hybrid molecules **5.13** containing colchicine/combrestatin A-4 analogs conjugated to a simplified pironetin scaffold.[29,30,114] These analogs were also found to be 1,000 to 10,000 fold less active than pironetin. While the Marco group synthesized a series of simplified analogs with groups other than non-conjugated olefin, the overall poor biological activity of these analogs could be due to the over-simplification of the pironetin scaffold. Due to the limited scope of the studies with analogs **5.3**, **5.11**-**5.13** and lack of systematic SAR studies around the non-conjugated olefin of pironetin, these previous reports did not provide significant insight into groups that would be tolerated instead of the non-conjugated olefin.



5.11

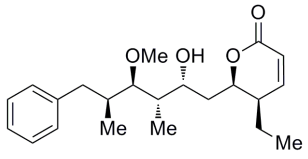
5.12a R = C_5H_{11}
5.12b C_9H_{19}
5.12c $C_{12}H_{25}$
5.12d Ph

5.13

Figure 5-6. Structure of pironetin analogs containing modification at the non-conjugated olefin.

5.3.2 Analog design and retrosynthesis. Since the SAR around the non-conjugated olefin had not been systematically evaluated, the first analog we sought to synthesize was phenylpironetin (**5.14**), as shown in Figure 5-7. Although an unsubstituted phenyl group

can also undergo cytochrome P450 metabolism, we decided to synthesize analog **5.14** to determine if an aromatic group would be tolerated at that position. If the phenyl analog **5.14** was found to be biologically active, we could synthesis additional analogs containing different substituent on the aromatic group. The addition of substituents on the phenyl group of analog **5.14** could potentially improve upon both the metabolic stability of the phenyl group and the overall potency of the molecule.

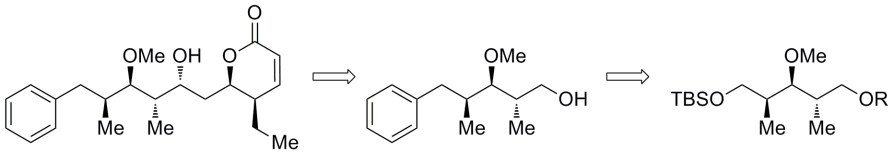


Phenylpironetin (**5.14**)

Figure 5-7. Structure of phenylpironetin (**5.14**).

We proposed that analog phenylpironetin (**5.14**) could be synthesized from alcohol **5.15** (Scheme 5-2). In our previous SAR studies, we have completed the synthesis of pironetin analogs from alcohols with similar structure to alcohol **5.15**. We proposed alcohol **5.15** could be derived from ether **5.16**. Intermediate **5.16a** was a previous intermediate in our synthesis in of pironetin analogs to evaluate the SAR at various positions of the α,β-unsaturated lactone.

Scheme 5-2. Retrosynthesis of phenylpironetin (**5.13**)

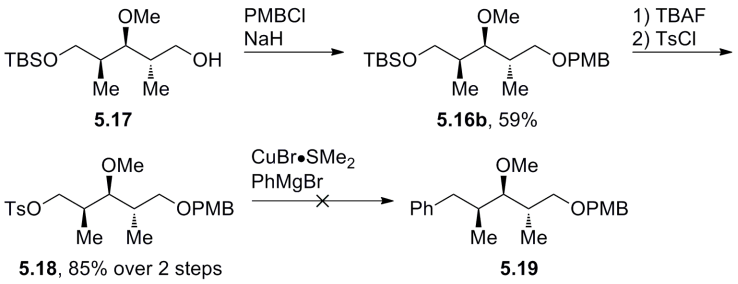


Phenylpironetin (**5.14**) **5.15** **5.16a** R = Bn **5.16b** PMB

5.3.3 Forward Synthesis. The primary challenge for the synthesis of analog **5.14** was the introduction of the phenyl ring. We initially proposed to introduce the phenyl group via a copper-catalyzed substitution reaction with a Grignard reagent. The silyl ether in

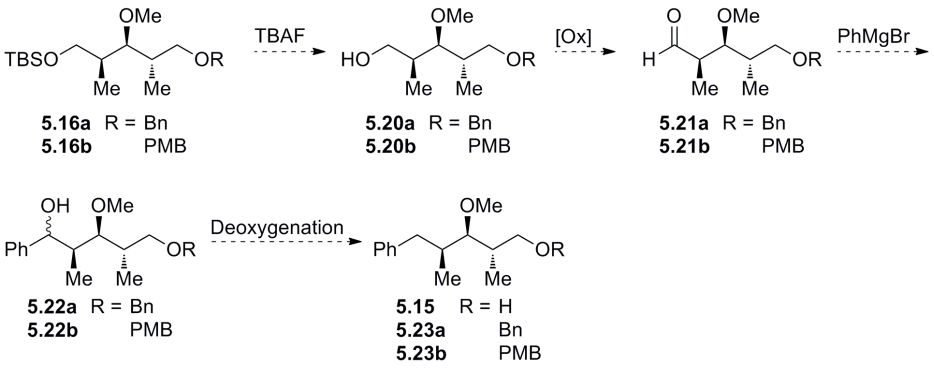
intermediate **5.16b** was converted to the primary tosylate **5.18**, as shown in Scheme 5-3; however, we were unable to couple the tosylate with phenyl magnesium bromide even in the presence of stoichiometric amounts of copper.

Scheme 5-3. Initial strategy to introduce the phenyl group via copper catalysis



Since we were unable to introduce the phenyl group via a substitution reaction, we explored alternative methods to introduce the phenyl group. As an alternative synthetic strategy, we proposed to introduce this group via Grignard addition to aldehyde **5.21** as shown in Scheme 5-4. Aldehyde **5.21** could be readily synthesized from intermediate **5.16**. Deoxygenation of the secondary alcohol **5.22** would result in intermediate **5.15** or **5.22**.

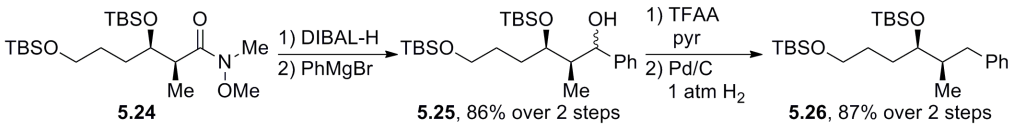
Scheme 5-4. Grignard addition/deoxygenation strategy for introduction of the phenyl group



When reviewing different methods for the deoxygenation of alcohol **5.22**, we found the deoxygenation of benzylic alcohols could be performed under a H_2 atmosphere in the

presence of a palladium catalyst. The palladium-catalyzed deoxygenation of the secondary benzylic alcohol would also remove the benzyl or PMB protecting group of intermediate **5.22**. Evans and coworker previously used this Grignard/deoxygenation strategy for the introduction of the phenyl group during their total synthesis of zaragozic acid C as shown in Scheme 5-5.[115] While the direct deoxygenation of secondary benzylic alcohols has been reported in the literature, Evans and coworkers converted benzylic alcohol **5.25** to the trifluoroacetate ester prior to hydrogenolysis. We chose to follow Evans' reported method since the hydrogenolysis was performed at room temperature under an atmospheric pressure of hydrogen.

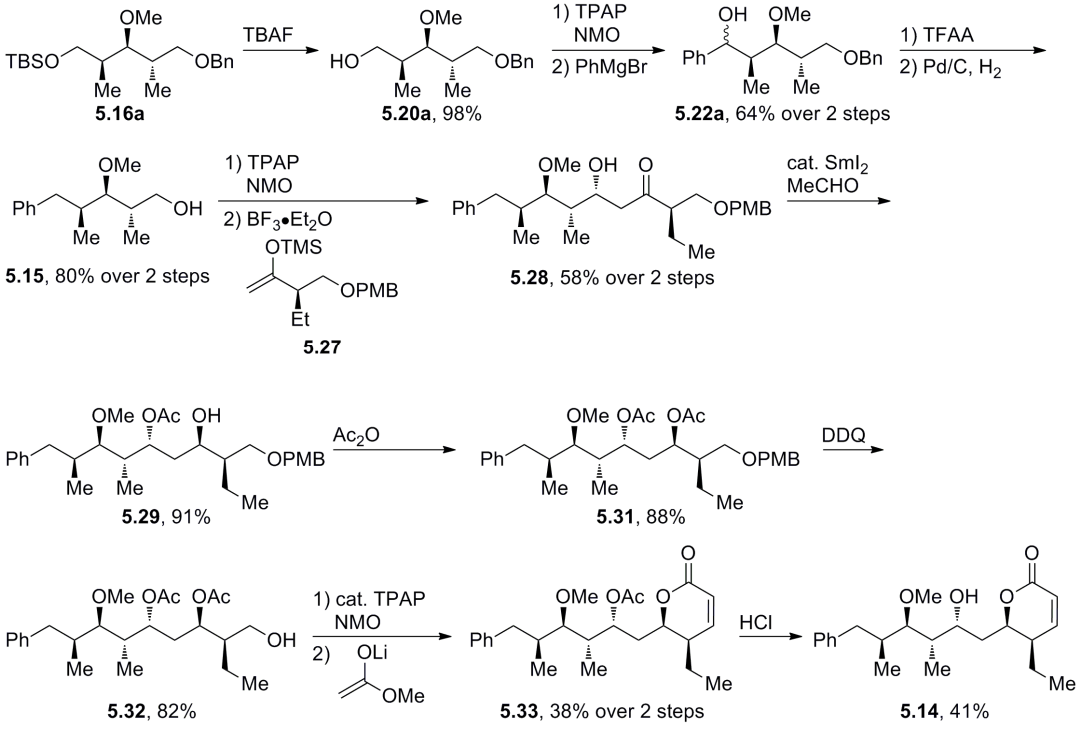
Scheme 5-5. Example of Grignard addition/deoxygenation strategy from Evans' zaragozic Acid C total synthesis



5.24 **5.25**, 86% over 2 steps **5.26**, 87% over 2 steps

Our forward synthesis of phenylpironetin **5.14** (Scheme 5-6), began with the removal of the TBS group in protected alcohol **5.16a**. Primary alcohol **5.20a** was oxidized to the aldehyde and treated with phenyl magnesium bromide to give benzylic secondary alcohol **5.22a**. Following Evans' method for the hydrogenolysis of benzylic secondary alcohols, the hydrogenolysis of the intermediate **5.22a** also resulted in hydrogenolysis of benzyl group resulting in desired alcohol **5.15**.

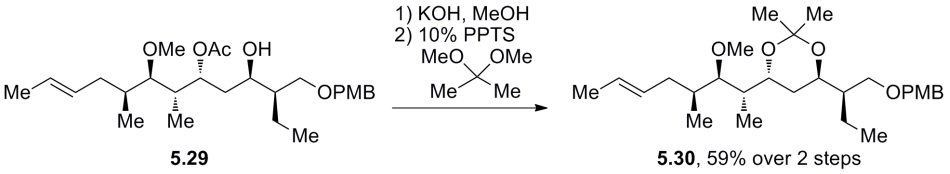
Scheme 5-6. Forward synthesis of phenylpironetin



At the time we completed the synthesis of alcohol **5.15**, we were synthesizing additional pironetin analogs for our SAR studies of the other positions of the molecule utilizing Keck's synthetic route for the total synthesis for pironetin. Thus, we chose to complete the synthesis of analog **5.14** following Keck's synthetic route.[50] Similar to Keck's pironetin total synthesis, the carbon backbone of intermediate phenylpironetin was synthesized via a Mukaiyama aldol between silyl enol ether **5.27** and the aldehyde resulting from the oxidation of alcohol **5.15**. Following the SmI_2-catalyzed disproportion reaction of β-hydroxyketone **5.28** to intermediate **5.29**, we confirmed the stereochemistry of secondary alcohol in intermediate **5.29** by converting this intermediate to the corresponding 1,3-diol acetonide **5.30** (Scheme 5-7); The ^{13}C NMR resonances of the acetonide were consistent with the chemical shifts reported for *anti*-1,3-diol acetonides (Figure 5-8).[64] The synthesis of phenylpironetin was completed following protection of

the secondary alcohol of **5.29** as the acetate ester and removal of the PMB protecting group. α,β-Unsaturated lactone **5.33** was synthesized from primary alcohol **5.32** following methodology developed by Keck and coworkers via a reaction between an β-acetoxy aldehyde and the lithium enolate of methyl acetate.[56] We completed the synthesis of analog **5.14** following acetate ester hydrolysis of intermediate **5.33**.

Scheme 5-7. Synthesis of acetonide **5.30** for ^{13}C NMR analysis



5.29 **5.30**, 59% over 2 steps

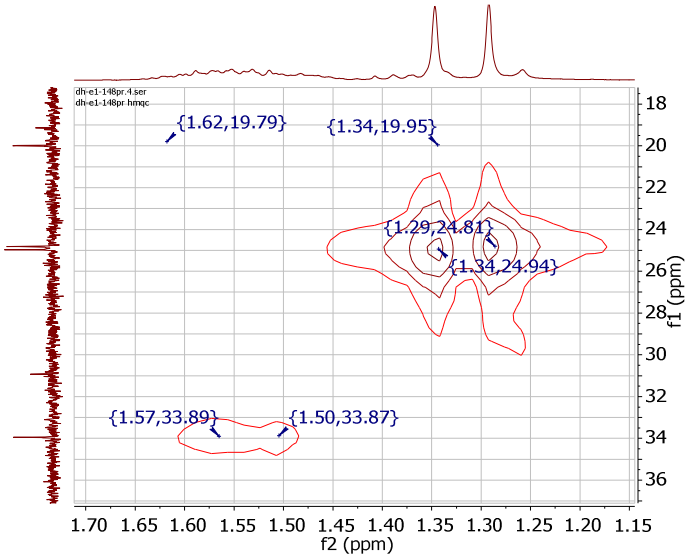


Figure 5-8. HMQC crosspeaks of acetonide **5.33**.

5.3.4 Biological activity and metabolic stability. We initially evaluated the antiproliferative of phenylpironetin against our previously utilized panel of ovarian cancer cell lines. Phenylpironetin was found to have comparable activity as pironetin as shown in Table 5-1 (Entries 1-3). Since phenylpironetin was an active analog, we sought to determine if replacing the non-conjugated olefin in pironetin with the phenyl group improved the natural products metabolic stability in human liver microsomes. While

phenylpironetin had minor improved stability in mouse liver microsomes, exchanging the non-conjugated olefin to a phenyl group decreased the metabolic stability; the calculated half-life in human liver microsomes decreased from 7 min to 5 min. We hypothesized the poor metabolic stability of phenylpironetin could be due to the rapid oxidation of the phenyl group. To evaluate if the phenyl group was the primary site of metabolism of analog **5.14**, we submitted phenylpironetin to Pharmaron for metabolite identification studies in human liver microsomes.

Table 5-1. Comparison of the biological activity and metabolic stability between pironetin and phenylpironetin

Entry		Pironetin (**5.1**)	Phenylpironetin (**5.14**)
1	GI_{50} (OVCAR5)[a,b]	21.9 ± 2.5 nM	57.5 ± 4.1 nM
2	GI_{50} (A2780)[a,b]	41.0 ± 1.5 nM	81.9 ± 5.0 nM
3	GI_{50} (A2780-CP)[a,c]	23.5 ± 1.3 nM	68.4 ± 2.0 nM
4	Liver Microsome Half-Life (Human)[d]	6.7 ± 0.8 min	5.4 ± 0.4 min
5	Liver Microsome Half-Life (Mouse)[d]	N/A[e]	4.4 ± 0.2 min

[a] Average of 2 experiments performed in triplicate ± SEM (n = 6)
[b] Drug-sensitive ovarian cancer cell line
[c] Cisplatin-resistant ovarian cancer cell line
[d] Average of 2 experiments performed by CEREP ± SEM
[e] Pironetin no detected ater 15 min

Pharmaron identified 17 metabolites following incubation of phenylpironetin in human liver microsomes over 15 min. The structures of some of the major metabolites are shown in Figure 5-9. Metabolites resulting from metabolism only on the phenyl group were detected in trace amounts. The primary site of metabolism was positions around the α,β-unsaturated lactone as shown metabolite **5.34**. Metabolites resulting from oxidation at the α,β-unsaturated lactone along with the side chains of the molecules, such as **5.35**-**5.37**, were also detected. While we did not predict metabolism at the α,β-unsaturated lactone and methyl side chains of phenylpironetin, this was not unexpected. In our previous metabolite identification study of pironetin performed by Pharmaron,

metabolite **5.7** resulting from oxidation around the non-conjugated olefin and other positions along the carbon skeleton increased over time during the 15 minute incubation in human liver microsomes.

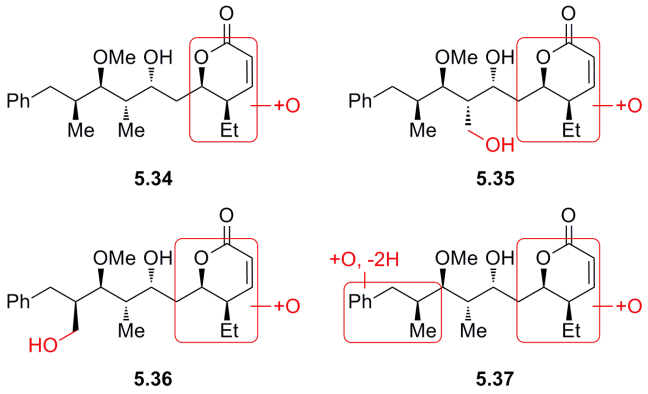


FIgure 5-9. Structure of select phenylpironetin metabolites following incubation in human liver microsomes.

5.4. Conclusion. To increase the *in vivo* efficacy of pironetin, we sought to synthesize analogs with improved metabolic stability. After identifying the non-conjugated olefin of pironetin as the primary site of metabolism, we synthesized analog **5.14** in which the non-conjugated olefin was replaced with a phenyl group. Phenylpironetin was found to have comparable antiproliferative activity as pironetin, but did not have improved metabolic stability. Metabolite identification assay with phenylpironetin **5.14** revealed the metabolism to occur at multiple positions around the α,β-unsaturated lactone and at the methyl side chains along the natural product's backbone. Although we modified the primary site of metabolism pironetin, additional modifications around the α,β-unsaturated lactone and substituents along the carbon backbone of pironetin are required to increase the natural product's metabolic stability.

Chapter 6. Experimental Procedures

6.1. General Experimental Procedures

6.1.1 General Materials and Chemistry Procedures. Normal-phase silica gel flash chromatography was conducted with Silicycle SilicaFlash® P60 silica gel or with preloaded Redisep® normal-phase silica flash columns. TLC was performed with Millipore Silica Gel 60 F254 or Analtech TLC Uniplates silica plate with florescent indicator (250 μm layer thickness). The product was visualized by UV light and/or staining with $KMnO_4$.

All NMR spectroscopy was conducted using either a Bruker Avance II 400 MHz instrument equipped with a BBO broadband probe or a Bruker Avance III 900 MHz instrument equipped with a TCI cryoprobe. NMR spectra were processed using MestReNova 9.0 (Metrelab Research S.L). Chemical shifts are reported in ppm and referenced to residual solvent peaks: $CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H NMR spectroscopy, 77 ppm for ^{13}C NMR spectroscopy. C_6H_6 in C_6D_6: 7.16 ^1H NMR spectroscopy, 128 ppm for ^{13}C NMR spectroscopy. CH_2Cl_2 in CD_2Cl_2: 5.32 ^1H NMR spectroscopy, 54 ppm for ^{13}C NMR spectroscopy. DMSO in DMSO-d_6: 2.50 ppm for ^1H NMR spectroscopy, 39.52 for ^{13}C NMR spectroscopy. Coupling constants are reported in Hertz. Mass spectrometry was performed on a Bruker BioTOF II. Optical rotations were measured on a Rudolph Research Analytical Autopol V polarimeter with a 100 mm sample cell. Melting points were measured on an Electrothermal IA9100.

All starting materials were purchased from commercial vendors and used without further purification unless noted. Phenylboronic acid was recrystallized from water.

Ethyl 2-(bis(*o*-tolyloxy)phosphoryl)acetate and samarium iodide were synthesized from commercial reagents instead of being purchased from commercial vendors. All reactions were performed with anhydrous solvent unless noted. Anhydrous solvents were degassed with nitrogen and passed through a column of activated alumina or molecular sieves (Solvent system from Inert Technologies).

6.1.2 HPLC and UPLC analysis methods. HPLC analysis was performed on the Water 2695 HPLC equipped with a Phenomnex Luna® 5 µm C18 100 Å, LC Column 150 × 4.6 mm. Samples were maintained at 10 °C and column was maintained at 25 °C. HPLC analyses were performed using the following method:

The mobile phase at a flow rate of 1 mL /min was increased from 50% MeCN/water to 70% MeCN/water over 30 min. The gradient was held at 70% MeCN/water for 1 min and then increased to 99% MeCN/water over 5 min and held for 5 min. The gradient was decreased back to 50% MeCN/water over 15 min and held for 10 min. Absorbance was monitored at 220 nm.

UPLC analysis was performed on the Water Acquity UPLC equipped with a BEH C18 column 1.7 µm, 2.1 × 50 mm. The column was maintained at 25 °C. The analyses were performed with mobile phase A (95% water, 5% MeCN, 0.1% formic acid) and mobile phase B (95% MeCN, 5% water, 0.1% formic acid) at a flow rate of 0.25 µL /min using the following gradient:

The mobile phase was increased from 95% mobile phase A and 5% mobile phase B to 50% mobile phase A and 50% mobile phase B over 1 min. The gradient was then increased to ramping to 5% mobile phase A and 95% mobile phase B over 4.5 min. The

mobile phase was then returned to 95% mobile phase A and 5% mobile phase B over 0.5 min. Absorbance was monitored at 214 nm.

6.1.3 Antiproliferative assays protocol. OVCAR5 cells were grown in Gibco ® RPMI 1640 media supplemented with 10% fetal bovine serum and 50 U/mL penicillin-streptomycin in at 37 °C incubator with 5% CO_2 atmosphere. A2780 and A2780-CP cells were grown in Gibco ® DMEM/F-12 media supplemented with 7.5% fetal bovine serum, 7.5% newborn calf serum, 1% non-essential amino acids, 4.8g/L HEPES, and 50 U/mL penicillin-streptomycin in at 37 °C incubator with 5% CO_2 atmosphere.

Assays were performed in Corning® 96 well clear flat bottom cell culture plates. Cells were plated at 2500 cell per well and incubated overnight to allow cells to adhere to the well. Solutions were of assayed compounds ranging from 200 μM to 0.2 nM were prepared in the growth media supplemented with 0.2% DMSO. Plated cells were dosed with each compound with final concentrations of compound ranging from 100 μM to 0.2 nM in growth media with 0.1 % DMSO and incubated for 48 h. Cell proliferation was measured with Promega CellTiter 96® Non-radioactive cell proliferation assay (cat. # G4100) following published protocols.[116] Absorbances were measured at 538 nm on a Molecular Devices Spectromax M2 plate reader. GI_{50} values were calculated by GraphPad Prism 5.

6.2 Chapter 2 experimental procedures

6.2.1 Pironetin extraction procedures

Sample extraction procedure from cell paste: The extraction procedure was adapted from a previously published procedure.[25] Frozen cell paste (2.3 kg) was suspended in acetone

(9 L) and stirred overnight via an overhead mechanical stirrer. The suspension was filtered and volatile materials were removed using a rotary evaporator to yield ~1.9 L of aqueous extract. The aqueous extract was divided into two aliquots of 0.95 L.

Each 0.95 L aliquot of aqueous extract was adjusted to pH = 7 with 3 M HCl. The aqueous layer was extracted once with EtOAc (0.8 L) and twice with EtOAc (0.5 L). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via vacuum filtration and volatile materials were removed using a rotary evaporator. The organic residues from each aliquot extraction were combined and stored in benzene prior to further purification.

The residues from separate extractions of 2.3 kg, 2.1 kg, 2.3 kg, and 2.4 kg were combined and suspended in hexanes (0.5 L). The solution was decanted through a Buchner funnel. The residual solid was dissolved in EtOAc (50 mL); Hexanes (0.5 L) was added to this solution. The removed via vacuum filtration and the residual solid was washed with hexanes. The filtrates from the different filtrations were combined and concentrated using a rotary evaporator. The crude extract was frozen in benzene prior to purification.

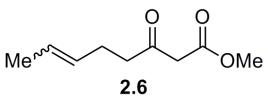
Sample extraction of fermentation broth: Frozen fermentation broth (17 kg) was thawed and filtered through cheese cloth followed by filtration through a coarse fritted funnel. The filtered fermentation broth was adjusted to pH 7 with 2 M HCl. Amberlite® XAD-16 resin (190 g) was shaken in water for 2 h. The resin suspension was filtered and the resin was washed three times with water. The resin was resuspended in methanol and shaken for 2 h. The resin suspension was filtered and washed three times with methanol.

The resin was added to the filtered fermentation broth. The resulting suspension was slowly stirred overnight via an overhead mechanical stirrer. The resin was recovered following filtration of the suspension through a coarse fritted funnel.

The recovered resin was split into 3 portions. Each portion was shaken in methanol for 2 h. The resin was recovered following filtration through a coarse fit and washing with methanol. The resin was resuspended in methanol and shaken for 2 h. The resin was recovered following filtration through a coarse fit and washed with methanol. The combined methanol filtrates from each portion of recovered resin were combined and filtered through a plug of Celite®. The resulting filtrate was concentrated using a rotary evaporator to ~200 mL. The resulting mixture was extracted six times with hexanes. The combined hexanes extracts were dried with anhydrous Na_2SO_4. The resulting salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was frozen in benzene prior to purification.

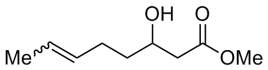
Purification of pironetin extracts: Extracts from the cell paste and fermentation broth were combined prior to purification. Extracts were initially purified via silica gel column chromatography (multiple columns of 40% EtOAc in hexanes). Final purification was performed via Combiflash equipped with a Biotage® C_{18} SNAP cartridge (10% 100% MeCN in water to 100% MeCN). The extraction from 165 kg of fermentation broth and 3 kg of frozen cell paste resulted in approximately 50 mg of pironetin.

6.2.2 Synthetic procedures and compound characterization data



2.6

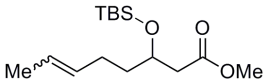
Methyl 3-Oxooct-6-enoate (2.6). To a suspension of sodium hydride (60% in mineral oil, 0.58 g, 15 mmol) in THF (33 mL) at 0 °C was added methyl acetoacetate (**2.5**, 1.4 mL, 13 mmol) dropwise. After stirring for 10 min, a solution of *n*-butyllithium (2.5 M in hexanes, 5.6 mL, 14 mmol) was added dropwise. After stirring an addition 10 min at 0 °C, a solution of crotyl bromide (1.5 mL, 15 mmol) in THF (3 mL) was added to the reaction. The reaction was warmed to room temperature and allowed to stir overnight. The reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (5% EtOAc in hexanes) to yield 1.60 g of product as a colorless oil (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 – 5.30 (m, 2H), 3.73 (s, 3H), 3.44 (s, 2H), 2.59 (t, J = 7.3 Hz, 2H), 2.39 – 2.16 (m, 2H), 1.63 (dq, J = 6.2, 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 167.6, 128.9, 128.1, 126.3, 125.47, 52.3, 49.1, 42.8, 26.4, 17.9.



2.7

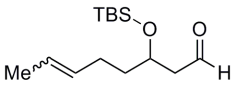
Methyl 3-Hydroxyoct-6-enoate (2.7). To a solution of β-keto-ester **2.6** (1.53 g, 8.88 mmol) in methanol (33 mL) in 0 °C was added sodium borohydride (0.44 g, 12 mmol). The reaction was warmed to room temperature and stirred for 6 h. The reaction was diluted with acetone (12 mL). Volatile materials were removed using a rotary evaporator. The crude material was diluted with EtOAc and saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted three times with EtOAc.

The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (15% EtOAc in hexanes) to yield 1.23 g of product as a colorless oil (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 – 5.31 (m, 2H), 4.01 (td, *J* = 8.0, 4.0 Hz, 1H), 3.71 (d, *J* = 1.1 Hz, 3H), 2.87 (dd, *J* = 12.6, 4.0 Hz, 1H), 2.60 – 2.32 (m, 2H), 2.26 – 1.89 (m, 2H), 1.73 – 1.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 130.4, 129.6, 125.6, 124.7, 77.2, 67.5, 51.7, 41.1, 41.1, 36.2, 36.1, 28.6, 17.9.



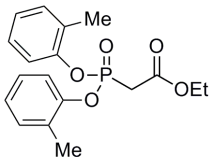
2.8

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)oct-6-enoate (2.8). To a solution of alcohol **2.7** (1.23 g, 7.14 mmol) in DMF (7.5 mL) was added imidazole (1.41 g, 20.7 mmol) followed by TBSCl (1.25 g, 8.29 mmol). After stirring at room temperature for 1.5 days, the reaction was diluted with saturated aqueous NH_4Cl. The mixture was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (8% EtOAc in hexanes) to yield 1.95 g of product as a colorless oil (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 – 5.33 (m, 2H), 4.23 – 4.06 (m, 1H), 3.66 (s, 2H), 2.57 – 2.37 (m, 2H), 2.10 – 1.93 (m, 2H), 1.71 – 1.47 (m, 5H), 0.86 (s, 6H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 130.7, 125.1, 69.0, 51.4, 42.5, 37.5, 28.1, 25.8, 17.9, -4.5, -4.8.



2.9

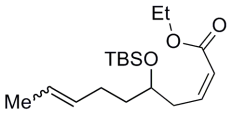
3-((*tert*-Butyldimethylsilyl)oxy)oct-6-enal (2.9). To a solution of methyl ester **2.8** (1.88 g, 6.56 mmol) in DCM (47 mL) at -78 °C, was added a solution of DIBAL-H (1 M in toluene, 13.1 mL, 13.1 mmol). After stirring at -78 °C for 30 min, the reaction was diluted with acetone (30 mL). The reaction was quenched with a solution of Rochelle (10 g) salt in water (22 mL). The reaction was warmed to room temperature and diluted with water and DCM. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (5% to 33% EtOAc in hexanes) to yield 1.42 g of product as a colorless oil (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, J = 2.5 Hz, 1H), 5.53 – 5.33 (m, 2H), 4.25 – 4.14 (m, 1H), 2.53 (ddd, J = 8.2, 5.8, 2.6 Hz, 2H), 2.09 – 1.96 (m, 2H), 1.71 – 1.51 (m, 5H), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H).



2.10

Ethyl 2-(Bis(*o*-tolyloxy)phosphoryl)acetate (2.10). The synthesis was adapted from previously published procedures.[117] To a solution of *o*-cresol (6.3 mL, 61 mmol) and triethylamine (8.9 mL, 64 mmol) in toluene (46 mL) at 0 °C was cannula transferred a solution of ethyl dichlorophosphite (4.6 g, 31 mmol) in ether (19 mL). The reaction was

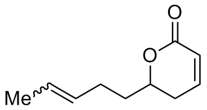
warmed to room temperature and stirred overnight. The reaction was filtered through a fritted funnel and washed with toluene. The filtrate was filtered through a plug of basic alumina. Volatile materials were removed using a rotary evaporator. To the crude phosphite at 120 °C was added ethyl bromoacetate (5.2 mL, 47 mmol) dropwise. After heating at 120 °C, the reaction was determined to be complete by ^{31}P NMR spectroscopy. The crude material was purified via silica gel flash chromatograph (25% EtOAc in hexanes) to yield 4.85 g of product as a colorless oil (45% yield). The resonances in the ^{1}H NMR of the product matched previously reported chemical shifts.[39]



2.11

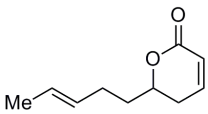
Ethyl 5-((*tert*-Butyldimethylsilyl)oxy)deca-2,8-dienoate (2.11). To a suspension of sodium hydride (60% in mineral oil, 0.21 g, 5.3 mmol) in THF (2 mL) at 0 °C was added a solution of phosphonate ester **2.10** (1.31 g, 3.76 mmol) over 5 min. The reaction was stirred at 0 °C for 15 min before cooling to -78 °C. A solution of aldehyde **2.9** (0.88 g, 3.4 mmol) in THF (1.7 mL) was added to reaction over 10 min. The reaction was stirred at -78 °C for 1 h before warming to room temperature. After an additional 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (5% EtOAc in hexanes) to yield 0.85 g of product as a 1:4 mixture of *E*:*Z* ratio for the conjugated olefin as a colorless oil (76% yield).

(*2Z*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 – 6.26 (m, 1H), 5.84 (dt, *J* = 11.6, 1.8 Hz, 1H), 5.57 – 5.24 (m, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.81 (p, *J* = 5.6 Hz, 1H), 3.03 – 2.68 (m, 2H), 2.20 – 1.88 (m, 2H), 1.63 (dt, *J* = 4.7, 1.3 Hz, 2H), 1.58 – 1.41 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 5H), 0.89 (d, *J* = 2.8 Hz, 10H), 0.05 (d, *J* = 2.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 146.6, 131.0, 124.9, 120.8, 100.0, 77.3, 77.2, 77.0, 76.7, 71.1, 71.0, 59.8, 37.1, 36.3, 28.5, 25.8, 22.9, 18.1, 17.9, 14.3, -4.5, -4.5.



2.12

6-(Pent-3-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (2.12). A solution of ester **3.11** (200. mg, 0.612 mmol) and PPTS (48 mg, 0.19 mmol) in EtOH (3 mL) was heated at 55 °C for 48 h. The reaction was cooled to room temperature and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (20% EtOAc in hexanes) to yield 71.7 mg of product as a colorless oil (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 9.8, 5.2, 3.3 Hz, 1H), 6.02 (dt, *J* = 9.8, 1.8 Hz, 1H), 5.65 – 5.28 (m, 2H), 4.43 (ddt, *J* = 9.7, 7.3, 5.6 Hz, 1H), 2.42 – 2.29 (m, 2H), 2.31 – 2.05 (m, 2H), 1.88 (dtd, *J* = 14.1, 8.2, 6.2 Hz, 1H), 1.74 – 1.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 144.9, 129.6, 126.2, 121.5, 77.3, 77.2, 77.0, 76.7, 34.6, 29.4, 27.7, 17.9.



2.2

(*E*)-6-(Pent-3-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (2.2). The mixture of lactone isomers **2.11** were separated with silica gel column chromatography with 10% wt silver

nitrate embedded silica gel. ^{1}H NMR (400 MHz, C_6D_6) δ 5.95 (ddd, *J* = 9.7, 5.9, 2.3 Hz, 1H), 5.92 – 5.81 (m, 1H), 5.54 – 5.29 (m, 2H), 3.91 (dddd, *J* = 11.7, 8.3, 4.8, 3.7 Hz, 1H), 2.22 – 1.92 (m, 2H), 1.66 (dq, *J* = 6.2, 1.3 Hz, 3H), 1.64 – 1.48 (m, 3H), 1.41 – 1.23 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6) δ 163.2, 143.7, 143.7, 130.3, 125.9, 121.8, 76.5, 34.9, 29.1, 28.1, 18.0. ^{13}C NMR (100 MHz, C_6D_6) δ 163.2, 143.7, 130.3, 125.9, 121.8, 76.5, 34.9, 29.1, 28.1, 18.0.

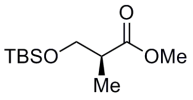
6.2.3 Serum Stability Assay. Human and mouse serum were purchased from Sigma Aldrich. Pironetin was analyzed by HPLC to be > 95% pure.

Sample procedure for serum stability assays. Pironetin (1.10 mg) in mouse serum (1.3 mL) and DMSO (1.3 μL) was shaken at 37 °C. Aliquots (100 μL) were taken after 10 min, 30 min, 1 h, 2 h, 4 h, 8 h, and 24 h for analysis of percent pironetin remaining in serum. Each aliquot was treated with a methanol solution (150 μL) of standard **2.2** (3.98 mg of lactone **2.2** in 5 mL methanol). The supernatant was separated from precipitated proteins via filtration using an Amicon ® Ultra 10K - 0.5 Centrifugal Filter Device. 75 μL of the filtrate was diluted with 75 μL of acetonitrile and analyzed via HPLC to calculate the amount of pironetin remaining in serum.

6.2.4 Incubation of pironetin with glutathione protocol. A solution of pironetin (6 mM) was prepared by dissolving pironetin (1.2 mg) in PBS (1x, pH 7.4, 0.6 mL) containing DMSO (0.1%). A solution of mono-ethyl glutathione (60 mM) was prepared by dissolving mono-ethyl glutathione (16 mg) in PBS (1x, pH 7.4, 0.8 mL) containing DMSO (0.1%). The pironetin solution (0.25 mL) was combined with the mono-ethyl glutathione solution (0.25 mL). The sample was shaken at 37 °C for 1 h. The sample

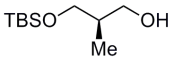
was extracted three times with EtOAc. The combine organic extracts were filtered through a plug of Celite®. The Celite® plug was rinsed with EtOAc. The filtrate was concentrated using a rotary evaporator. The residue was submitted to Sara Coulup for LC-MS/MS analysis for the detection of glutathione adducts.

6.3 Chapter 3 experimental procedures



3.29

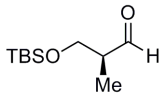
(*S*)-Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanoate (3.29). The product was synthesized following a previously reported procedure.[118] To a solution of (*S*)-Roche ester **3.28** (1.25 g, 10.6 mmol) in DCM (44 mL) was added imidazole (0.86 g, 13 mmol) followed by TBSCl (1.75 g, 11.6 mmol). The reaction was stirred at room temperature overnight. The reaction was filtered through a fritted funnel. The filtrate was concentrated using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (5% ether in hexanes) to yield 2.36 g of product as a colorless oil (96% yield). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[118]



3.30

(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol (3.30). The product was synthesized following a previously reported procedure for the (*S*)-enantiomer.[119] To a solution of ester 3.29 (1.74 g, 7.47 mmol) in DCM (75 mL) at -78 °C was cannula transferred a solution of DIBAL-H (1 M in toluene, 15.7 mL, 15.7 mmol) over 25 min.

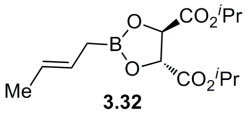
The reaction was stirred at -78 °C for 10 min and then warmed to -40 °C and stirred for an additional 1 h. The reaction was cooled to -78 °C and then quenched with MeOH (2.1 mL) and stirred for 10 min. The reaction was poured into DCM (50 mL) and saturated aqueous Rochelle salt (50 mL) and stirred for 2 h. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (10% to 15% EtOAc in hexanes) to yield 1.41 g of product as a colorless oil (92% yield). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[119]



3.31

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanal (3.31). The product was synthesized following previously a reported procedure for the (*R*)-enantiomer.[120] To a solution of oxalyl chloride (2.1 mL, 24 mmol) in DCM (154 mL) at -78 °C was added dimethylsulfoxide (3.4 mL, 48 mmol) dropwise. After stirring the reaction at -78 °C for 10 min, a solution of alcohol **3.30** (3.30 g, 16.2 mmol) in DCM (6.4 mL) was added dropwise. After stirring the reaction at -78 °C for an additional 30 min, TEA (14.6 mL, 105 mmol) was added dropwise and stirred at -78 °C for an additional 1 h. The reaction was warmed to -40 °C and diluted with DCM and quenched with saturated aqueous NH_4Cl. The reaction was warmed to room temperature and diluted with ether. The layers were separated and the aqueous layers were extracted twice with ether. The

combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (6% EtOAc in hexanes) to yield 3.01 g of product as a colorless oil (92% yield). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[120]

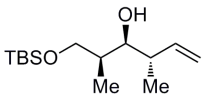


3.32

Diisopropyl (*4R,5R*)-2-((*E*)-But-2-en-1-yl)-1,3,2-dioxaborolane-4,5-dicarboxylate (3.32). The product was synthesized following a previously reported procedure[121] To a suspension of potassium *tert*-butoxide (7.04 g, 62.7 mmol) in THF (52 mL) at -78 °C was cannula transferred *trans*-2-butene (~6.2 mL). To the reaction was cannula transferred a solution of *n*-butyllithium (1.95 M in hexanes, 32.2 mL, 62.7 mmol) over 20 min. The reaction was warmed to -50 °C and stirred for 15 min and recooled to -78 °C. Triisopropyl borate (14.6 mL, 62.7 mmol) was cannula transferred to the reaction over 30 min and stirred at -78 °C for 15 min. The reaction was poured into at separatory funnel containing 1 M HCl (110 mL) saturated with NaCl. The pH of the solution was measured to ensure it was pH = 1. A solution of (+)-diisopropyl L-tartrate (14.7 g, 62.7 mmol) dissolved in ether (22 mL) was added to the separatory funnel. The layers were separated and the organic layer was extracted four times with ether (30 mL). The combined organic layers were stirred with anhydrous $MgSO_4$ for 2 h. The salts were removed via gravity filtration and volatile materials were removed using a rotary

evaporator. Residual volatile materials were removed under high vacuum to yield 17.1 g of crude material. The crude material was dissolved in toluene (20 mL) to give 34 mL of solution of crotylation reagent **3.32**.

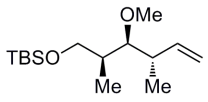
For determining the concentration of reagent **3.32**, to 1,3,5-trimethoxybenzene (14 mg, 0.083 mmol) and cyclohexanescarboxaldehyde (0.10 mL, 0.83 mmol) was added a the solution of crotylation reagent **3.32** (0.2 mL) and stirred at room temperature for 45 min. A suspension of $NaBH_4$ (34 mg, 0.90 mmol) in EtOH (1 mL) was added to the reaction and stirred for an additional 45 min. A solution of sodium hydroxide (3 M, 2 mL) was then added to the reaction and stirred for an additional 1 h. The reaction was diluted with ether and the layers were separated. The organic layer was concentrated under reduced pressure. ^{1}H NMR analysis of the crude material showed the solution of reagent **3.32** to be 0.6 M based on the relative amount of (1,2-*anti*)-1-cyclohexyl-2-methylbut-3-en-1-ol and 1,3,5-trimethoxybenzene.



3.27

(*2S,3S,4S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (3.27). The product was synthesized following a previously reported procedure.[58] A solution of crotylation reagent **3.32** (0.6 M in toluene, 29 mL, 18 mmol) was stirred over powdered 4 Å molecular sieves (2 g) for 10 min then cooled to -78 °C. A solution of aldehyde **3.31** (2.37 g, 11.7 mmol) in toluene (10 mL) was cannula transferred to the reaction over 25 min. The reaction was stirred at -78 °C for 7 h. The reaction was filtered through a plug of Celite® and the filtrate was diluted with ether and water. The layers were separated

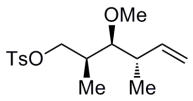
and the aqueous layer was extract three times with ether. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was dissolved in ether (150 mL) and aqueous KOH (1 M, 150 mL) and stirred overnight. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (5% ether in hexanes). Impure material was further purified three times with via silica gel flash chromatograph (5% ether in hexanes). The combined product from 4 columns yielded 2.35 g of as a colorless oil product as a colorless oil (78% yield). The resonances in the ^1H NMR spectrum of the product matched previously reported chemical shifts.[121]



3.33

***tert*-Butyl(((*2S,3S,4S*)-3-methoxy-2,4-dimethylhex-5-en-1-yl)oxy)dimethylsilane (3.33).** To a suspension of sodium hydride (60% in mineral oil, 2.1 g, 52 mmol) in THF (90 mL) was added a solution of alcohol **3.27** (2.32 g, 8.98 mmol) in THF (10.5 mL). After stirring for 1.5 h, iodomethane (2.8 mL, 45 mmol) was added to the reaction and the reaction was stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine

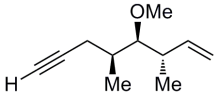
and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (2% ether in hexanes) to yield 2.28 g of product as a colorless oil (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.7, 10.3, 7.8 Hz, 1H), 5.19 – 4.89 (m, 2H), 3.65 – 3.42 (m, 2H), 3.40 (s, 3H), 3.08 (dd, *J* = 6.8, 4.1 Hz, 1H), 2.40 (q, *J* = 7.1 Hz, 1H), 1.96 – 1.68 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 114.0, 85.2, 77.3, 77.0, 76.7, 65.5, 60.9, 40.9, 38.3, 25.9, 25.9, 18.2, 17.1, 11.1, -5.4. HRMS calc *m*/*z* $[C_{15}H_{32}O_2Si + Na]^+$: 295.2064, found: 295.2048.



3.26

(*2S,3S,4S*)-3-Methoxy-2,4-dimethylhex-5-en-1-yl 4-Methylbenzenesulfonate (3.26). To a solution of ether **3.33** (0.109 g, 0.400 mmol) in THF (0.7 mL) was added TBAF (1 M in THF, 2 mL, 2 mmol). After stirring for 3 h, the reaction was diluted with EtOAc and diluted with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was dissolved in pyridine (2.7 mL) followed by addition of TsCl (229 mg, 1.20 mmol). The reaction was stirred overnight and then poured into water and diluted with EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The

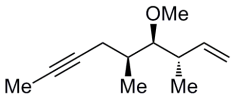
salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (10% EtOAc in hexanes) to yield 0.115 g of product as a colorless oil (92% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.87 – 5.72 (m, 1H), 5.12 – 4.88 (m, 2H), 4.08 – 3.82 (m, 2H), 3.31 (s, 3H), 2.98 (dd, *J* = 6.8, 4.1 Hz, 1H), 2.45 (s, 3H), 2.30 (q, *J* = 7.2 Hz, 1H), 2.13 – 1.88 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 141.0, 133.1, 129.8, 127.9, 114.7, 84.2, 77.3, 77.0, 76.7, 72.7, 60.8, 40.7, 35.6, 10.8.



3.35

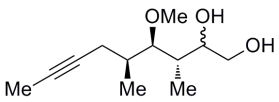
(*3S,4R,5S*)-4-Methoxy-3,5-dimethyloct-1-en-7-yne (3.35). Inside a dry box under a N_2 atmosphere, tosylate **3.26** (1.00 g, 3.20 mmol) was dissolved in dimethylsulfoxide (9.7 mL). Lithium acetylide ethylenediamine complex **3.34** (90%, 0.54 g, 5.3 mmol) was added to the solution. The reaction was removed from the dry box and stirred for 1.5 h. The reaction was diluted with ether and quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (2% ether in pentane) to yield 0.414 g of product as a colorless oil (78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.3, 10.3, 8.0 Hz, 1H), 5.19 – 4.93 (m, 2H), 3.44 (s, 3H), 3.01 (dd, *J* = 6.3, 4.9 Hz, 1H), 2.40 (h, *J* = 7.1 Hz, 1H), 2.22 (qdd, *J* = 16.8, 6.7, 2.6

Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.88 (qd, *J* = 6.8, 4.9 Hz, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 114.4, 87.3, 83.3, 69.3, 61.3, 40.9, 35.3, 23.2, 17.3, 14.3.



3.25

(*3S,4R,5S*)-4-Methoxy-3,5-dimethylnon-1-en-7-yne (3.25). To a solution of alkyne **3.35** (0.110 g, 0.662 mmol) in THF (3.9 mL) at 0 °C, was added a solution of *n*-butyllithium (2.2 M in hexanes, 0.50 mL, 1.1 mmol). After stirring for 20 min at 0 °C, iodomethane (0.14 mL, 2.2 mmol) was added to the reaction. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (2% ether in pentane) to yield 0.106 g of product as a colorless oil (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.3, 10.3, 8.0 Hz, 1H), 5.15 – 4.92 (m, 2H), 3.44 (s, 3H), 2.98 (dd, *J* = 6.3, 5.0 Hz, 1H), 2.40 (dq, *J* = 7.8, 6.7 Hz, 1H), 2.14 (ddddt, *J* = 18.9, 14.3, 11.8, 7.2, 2.6 Hz, 2H), 1.85 – 1.74 (m, 4H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 114.3, 87.6, 77.8, 76.5, 61.3, 40.9, 35.7, 23.6, 17.3, 14.4, 3.5.



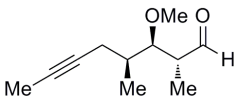
3.36

(*3S,4R,5S*)-4-Methoxy-3,5-dimethylnon-7-yne-1,2-diol (3.36). Table 3-1, entry 1: To a solution of alkene **3.25** (30. mg, 0.17 mmol) in *tert*-butanol (0.5 mL), THF (0.5 mL), and water (0.1 mL) at 0 °C was added NMO (40. mg, 0.34 mmol) followed by a solution of OsO_4 (2.5% in *tert*-butanol, 0.10 mL, 0.0080 mmol). The reaction was warmed to room temperature and stirred for 5 h. Additional NMO (15 mg, 0.13 mmol) was added to the reaction. After stirring for an additional 1 h, sodium metabisulfite (250 mg) was added to the reaction. After stirring for an additional 30 min, the salts were removed via gravity filtration. The solid was washed with EtOAc, and the filtrate was concentrated using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (4% methanol in DCM) to yield 22.7 mg of product as a colorless oil (64% yield). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 – 3.67 (m, 2H), 3.60 – 3.51 (m, 4H), 3.31 (dd, J = 8.5, 2.7 Hz, 1H), 2.29 – 2.13 (m, 2H), 2.00 – 1.84 (m, 2H), 1.81 (t, J = 2.6 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H).

Table 3-1, entry 2: To a solution of alkene **3.25** (40. mg, 0.22 mmol) in acetone (0.5 mL) and water (1 mL) at 0 °C was added NMO (31 mg, 0.26 mmol) followed by solution of OsO_4 (4% in water, 0.070 mL, 0.011 mmol). The reaction was warmed to room temperature and stirred for 2.5 h. Additional NMO (31 mg, 0.26 mmol) was added to the reaction. After stirring for an additional 3 h, the reaction was quenched with saturated aqueous sodium sulfite and stirred for 30 min. The mixture was concentrated using a rotary evaporator. The crude mixture was suspended in saturated aqueous sodium thiosulfate and the solution was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were

removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (4% methanol in DCM) to yield 21.8 mg of product as a colorless oil (45% yield).

Table 3-1, entry 3: A suspension of AD-mix-α (230 mg) was stirred in *tert*-butanol (0.9 mL) and water (1 mL) at room temperature before cooling to 0 °C. A solution of alkene **3.25** (30. mg, 0.17 mmol) in *tert*-butanol (0.2 mL) was added to the reaction. The flask containing alkene **3.25** was rinsed with additional *tert*-butanol (0.2 mL) which was added to the reaction and stirred overnight at 0 °C. After 20 h, an additional portion of AD-mix-α (480 mg) was added to the reaction and the reaction was stirred at 0 °C overnight. The reaction was quenched with saturated aqueous sodium sulfite and warmed to room temperature. After stirring for 30 min, saturated aqueous sodium thiosulfate was added to the reaction. The mixture was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (4% methanol in DCM) to yield 27.6 mg of product as a colorless oil (78% yield).



3.24

(*2R,3R,4S*)-3-Methoxy-2,4-dimethyloct-6-ynal (3.24). A suspension of AD-mix-α (580 mg) was stirred in *tert*-butanol (1.7 mL) and water (2 mL) at room temperature before cooling to 0 °C. A solution of alkene **3.25** (75 mg, 0.42 mmol) in *tert*-butanol (0.3 mL) was added to the reaction. The flask containing alkene **3.25** was rinsed with additional

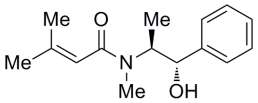
tert-butanol (0.3 mL) which was added to the reaction and stirred overnight at 0 °C. After 16 h, an additional portion of AD-mix-α (580 mg) was added to the reaction and the reaction was stirred at 0 °C for an additional 24 h. Sodium sulfite (1.06 g) was added to the reaction and warmed to room temperature and stirred for 1.5 h. The reaction was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. To a solution of crude diol **3.36** in DCM (4.2 mL), was added (diacetoxyiodo)benzene (0.16 g, 0.50 mmol). After 1.5 h, the reaction was concentrated using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (20% ether in hexanes) to yield 45.2 mg of product as a colorless oil (60% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 2.4 Hz, 1H), 3.48 (dd, *J* = 7.4, 3.8 Hz, 1H), 3.44 (s, 3H), 2.63 (pd, *J* = 7.1, 2.4 Hz, 1H), 2.30 – 2.08 (m, 2H), 1.85 (dtd, *J* = 7.5, 6.6, 3.8 Hz, 1H), 1.79 (t, *J* = 2.6 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H).

Table 3-2, entry 1: To a solution of diol **3.36** (22.7 mg, 0.106 mmol) in THF (0.6 mL) and pH 7 phosphate buffer (0.15 mL) was added sodium periodate (34 mg, 0.16 mmol). After stirring for 3 h, additional sodium periodate (20. mg, 0.094 mmol) was added to the reaction. After stirring an additional 2.5 h, the suspension was filtered through a cotton plug. The solid was rinsed with EtOAc. The filtrate was washed with water, brine and then dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (4:1 hexanes:ether) to yield 11.6 mg of

product as a colorless oil (60% yield).

Table 3-2, entry 2: To a solution of diol **3.36** (21.8 mg, 0.102 mmol) in DCM (1 mL), was added (diacetoxyiodo)benzene (39 mg, 0.12 mmol). After 2 h, the reaction was concentrated using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (20% ether in hexanes) to yield 12.5 mg of product as a colorless oil (67% yield).

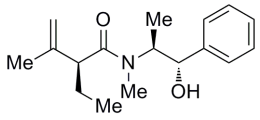
Table 3-2, entry 3: To a solution of diol **3.36** (27.6 mg, 0.129 mmol) in DCM (1.3 mL) was added lead (IV) acetate (68 mg, 0.15 mmol). After stirring for 1 h, additional lead (IV) acetate (34 mg, 0.077 mmol) was added to the reaction. After stirring an additional 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was filtered through Celite® and the filtrate was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (4:1 hexanes:ether) to yield 11.2 mg of product as a colorless oil (48% yield).



3.38

***N*-((*1S,2S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,3-dimethylbut-2-enamide (3.38).** The product was synthesized following a previously reported procedure.[50] To a solution of (*1S*,*2S*)-(+)-pseudoephedrine (**3.37**, 1.0 g, 6.1 mmol) and triethylamine (1.1 mL, 7.9 mmol) in THF (15 mL) at 0 °C was added 3,3-dimethylacryloyl chloride (0.78 mL, 7.0 mmol). After stirring 1 h at 0 °C, the reaction was slowly quenched with water. The

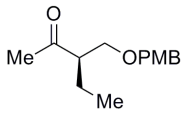
reaction was poured into brine and extracted four times with EtOAc. The combined organic layers were dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was recrystallized from hot toluene to yield 1.24 g of product as a white solid (83% yield). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[50]



3.39

(*S*)-2-Ethyl-*N*-((*1S,2S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,3-dimethylbut-3-enamide (3.39). The product was synthesized following a previously reported procedure.[50] To a suspension of lithium chloride (0.25 g, 5.9 mmol) and diisopropylamine (0.32 mL, 2.3 mmol) in THF (1.3 mL) at -78 °C was added a solution of *n*-butyllithium (2.2 M in hexanes, 1.0 mL, 2.2 mmol). The reaction was warmed to room temperature and stirred for 10 min and then cooled to -78 °C. A suspension of amide **3.38** (0.25 g, 1.0 mmol) in THF (1.75 mL) was added to the reaction. The flask containing the suspension of amide **3.38** was rinsed with additional THF (0.5 mL) which was added to the reaction. The reaction was stirred at -78 °C for 1 h and then warmed to 0 °C and stirred for 15 min. The reaction was warmed to room temperature and stirred and additional 15 min before cooling to 0 °C. Iodoethane (0.16 mL, 2.0 mmol) was added dropwise to the reaction and stirred for an additional 2 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity

filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (25% to 40% EtOAc in hexanes) to yield 0.21 g of product as a colorless oil (78% yield). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[50]



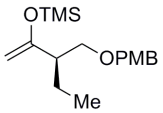
3.40

(*R*)-3-(((4-Methoxybenzyl)oxy)methyl)pentan-2-one (3.40). The product was synthesized by adapting previously reported procedures.[50] To a solution of diisopropylamine (0.60 mL, 3.9 mmol) in THF (2.1 mL) at 0 °C was added a solution of *n*-butyllithium (2.2 M in hexanes, 1.7 mL, 3.7 mmol) and stirred at 0 °C for 5 min. Borane-ammonia complex (90%, 0.13 g, 3.9 mmol) was added to the reaction and the reaction was stirred at 0 °C for an additional 20 min. The reaction was warmed to room temperature and stirred for 30 min before cooling to 0 °C. A solution of amide **3.39** (0.20 g, 0.74 mmol) in THF (0.6 mL) was added to the reaction. The flask containing the solution of amide **3.39** was rinsed with additional THF (0.4 mL) which was added to the reaction. The reaction was stirred at 0 °C for 20 min before warming to room temperature and stirred for an additional 2 h. The reaction was cooled to 0 °C, and 3 M HCl (8.4 mL) was added dropwise via an addition funnel. After stirring at 0 °C for 25 min, the reaction was warmed to room temperature and stirred for an additional 15 min. The reaction was extracted three times with 30% ether in pentane. The combined organic layers were concentrated using a rotary evaporator to ~1.2 mL. The solution of the crude alcohol was added dropwise to a suspension of potassium hydride (30% in mineral oil,

0.20 g, 0.14 mmol) in THF (1.5 mL) at -20 °C. The flask containing the alcohol solution was rinsed with additional THF (0.5 mL) which was added to the reaction. After stirring at -20 °C for 20 min, PMBCl (0.16 mL, 1.2 mmol) was added to the reaction. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with ice and diluted with saturated aqueous NH_4Cl. The mixture was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator.

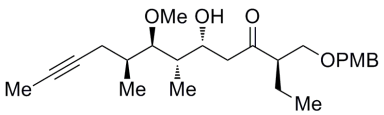
To a solution of the crude material in THF (2.5 mL), *tert*-butanol (2.5 mL), and water (0.5 mL) at 0 °C, was added NMO (0.16 g, 1.4 mmol). A solution of osmium tetraoxide (2.5% in *tert*-butanol, 0.44 mL, 0.035 mmol) was added to the reaction. The reaction was warmed to room temperature and stirred for 5 h. Sodium metabisulfite (1 g) was added to the reaction and the suspension was stirred for 45 min until the reaction became clear. The suspension was filtered and solids were washed with EtOAc. The filtrate was concentrated via rotary evaporator to yield the crude diol. To a solution of crude diol in THF (3.8 mL) and water (1 mL) was added sodium periodate (0.20 g, 0.91 mmol). After stirring at room temperature for 3 h, the reaction was filtered and the solid was washed with EtOAc. The filtrate was dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (15% EtOAc in hexanes) to yield 97.9 mg of product as a colorless oil (56% yield over 4 steps). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously

reported chemical shifts.[50]



3.20

(*R*)-((3-(((4-Methoxybenzyl)oxy)methyl)pent-1-en-2-yl)oxy)trimethylsilane (3.20). The product was synthesized following a previously reported procedure.[50] To solution of LiHMDS (1 M in hexanes, 2.1 mL, 2.1 mmol) in THF (13 mL) at -78 °C, was added a solution of ketone **3.40** (0.20 g, 0.85 mmol) in THF (0.6 mL). The flask containing ketone **3.40** was rinsed with additional THF (0.4 mL) which was added to the reaction. The reaction was stirred at -78 °C and stirred for 15 min. The reaction was quenched with a TEA/TMSCl (1:1 mixture filtered through Celite®, 0.27 mL) and stirred at -78 °C for 15 min. The reaction was warmed to room temperature and diluted with ether (3.5 mL). The reaction was concentrated to ~ 1 mL using a rotary evaporator and diluted with a 4:1 mixture of hexanes:ether (10 mL). The suspension was concentrated using a rotary evaporator. The crude material was suspended in a 4:1 mixture of hexanes:ether (10 mL) and concentrated under rotary evaporator twice. The crude material was suspended in a 4:1 mixture of hexanes:ether (10 mL) and filtered through a plug of Celite®. The filtrate was concentrated using a rotary evaporator to yield 0.20 g of crude silyl enol ether. The silyl enol ether was used without further purification. The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[50]



3.23

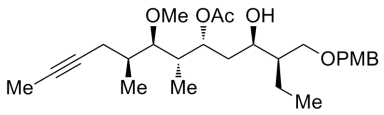
(*3R,6R,7S,8R,9S*)-6-Hydroxy-8-methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-

dimethyltridec-11-yn-4-one (3.23). To a solution of aldehyde **3.24** (78.7 mg, 0.432 mmol) and silyl enol ether (0.20 g crude, 0.65 mmol) in DCM (3.9 mL) at -90 °C (methanol:*lq* N_2 bath) was added BF_3•Et_2O solution (1 M in DCM, 0.7 mL, 0.7 mmol). The reaction was stirred at -90 °C for 2 h before quenching with saturated aqueous $NaHCO_3$. The mixture was warmed to room temperature and extracted three times with EtOAc and once with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph to yield 0.115 g of product as a colorless oil (64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 2H), 6.89 – 6.82 (m, 2H), 4.46 – 4.36 (m, 3H), 3.80 (s, 3H), 3.59 (t, *J* = 8.8 Hz, 1H), 3.52 – 3.44 (m, 4H), 3.28 (dd, *J* = 7.8, 4.0 Hz, 1H), 2.87 – 2.67 (m, 2H), 2.47 (dd, *J* = 17.0, 3.3 Hz, 1H), 2.35 – 2.09 (m, 2H), 1.89 (qd, *J* = 6.8, 4.0 Hz, 1H), 1.79 (t, *J* = 2.6 Hz, 3H), 1.74 – 1.50 (m, 2H), 1.50 – 1.35 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 159.2, 129.9, 129.3, 113.8, 85.7, 77.8, 76.6, 73.0, 70.6, 66.5, 61.8, 55.2, 54.3, 48.2, 39.8, 35.4, 23.9, 21.6, 13.6, 11.7, 10.3, 3.5.

Samarium Iodide

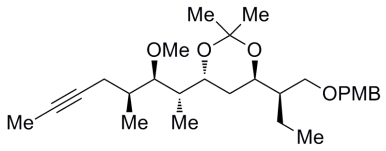
The product was synthesized following a previously reported procedure.[122] Inside a dry box under a N_2 atmosphere, samarium powder (90. mg, 0.60 mmol) and THF (3 mL) were added to a round bottom flask. Iodine (76 mg, 0.30 mmol) was added to the flask. The reaction was sealed with a glass stopper and covered with aluminum foil. The flask was removed from the glovebox and stirred at 60 °C overnight. The flask was cooled to

room temperature and the solution was stored in the dry box. The solution was titrated with 2-heptanone to calculate the concentration.[123]



3.41

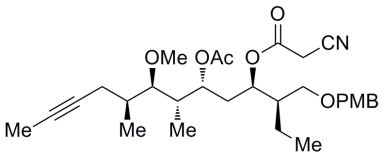
(*3R,4R,6R,7S,8R,9S*)-4-Hydroxy-8-methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-dimethyltridec-11-yn-6-yl Acetate (3.41). To a solution of ketone **3.23** (60.7 mg, 0.145 mmol) and acetaldehyde (0.070 mL, 1.2 mmol) in THF (0.6 mL) at -15 °C was added dropwise a solution of SmI_2 (0.075 M in THF, 0.78 mL, 0.059 mmol) dropwise. The reaction was stirred at -15 °C for 1 h before quenching with saturated aqueous $NaHCO_3$. The mixture was warmed to room temperature and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (4:1 hexanes:EtOAc) to yield 58.7 mg of product as a colorless oil (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.92 – 6.82 (m, 2H), 5.38 (ddd, *J* = 9.6, 3.9, 1.8 Hz, 1H), 4.51 – 4.36 (ABq, 2H), 3.80 (s, 3H), 3.68 (dt, *J* = 10.5, 3.0 Hz, 1H), 3.57 – 3.44 (m, 3H), 3.41 (s, 3H), 3.05 (dd, *J* = 9.4, 2.3 Hz, 1H), 2.28 – 2.10 (m, 2H), 2.08 (s, 3H), 1.92 – 1.76 (m, 4H), 1.76 – 1.64 (m, 2H), 1.64 – 1.51 (m, 2H), 1.53 – 1.28 (m, 3H), 0.94 – 0.83 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 159.1, 130.4, 129.2, 113.7, 83.9, 78.2, 76.6, 72.9, 71.8, 70.7, 68.8, 61.5, 55.2, 45.5, 40.2, 37.6, 35.7, 24.5, 21.1, 19.1, 12.8, 12.3, 10.4, 3.4.



3.42

(*4R,6R*)-4-((*2S,3R,4S*)-3-Methoxy-4-methyloct-6-yn-2-yl)-6-((*R*)-1-((4-methoxybenzyl)oxy)butan-2-yl)-2,2-dimethyl-1,3-dioxane (3.42). To a solution of alcohol **3.41** (16 mg, 0.035 mmol) in methanol (0.5 mL) was added potassium hydroxide (3 mg, 0.05 mmol) and stirred at room temperature. After 4 h, additional potassium hydroxide (10. mg, 0.18 mmol) was added to the reaction and the reaction was stirred for an additional 1 h. The reaction was quenched with saturated aqueous NH_4Cl, and extracted four times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude diol was stirred overnight in 1,3-dimethoxypropane (1 mL) and PPTS (1 mg). The reaction was diluted with DCM (2 mL) and quench with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (9:1 hexanes:EtOAc) to yield 9.2 mg of product as a colorless oil (58% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 6.92 – 6.83 (m, 2H), 4.49 – 4.32 (m, 2H), 4.08 (td, *J* = 8.0, 2.4 Hz, 1H), 3.88 – 3.75 (m, 4H), 3.47 (s, 3H), 3.46 – 3.36 (m, 2H), 3.24 (dd, *J* = 9.3, 2.0 Hz, 1H), 2.26 – 2.07 (m, 2H), 1.84 (td, *J* = 7.1, 2.0 Hz, 1H), 1.80 (t, *J* = 2.5 Hz, 3H), 1.67 – 1.59 (m, 3H), 1.55 – 1.44 (m, 2H), 1.35 (s, 4H), 1.30 (s,

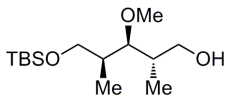
4H), 0.95 – 0.85 (m, 6H), 0.82 (d, J = 7.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.7, 129.3, 113.7, 100.0, 83.9, 78.5, 76.3, 72.8, 68.5, 67.3, 65.4, 61.3, 55.3, 45.0, 41.1, 35.7, 34.0, 30.3, 29.7, 25.0, 24.9, 24.7, 20.0, 12.7, 11.7, 10.0, 3.5.



3.43

(*3R,4R,6R,7S,8R,9S*)-6-Acetoxy-8-methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-dimethyltridec-11-yn-4-yl 2-Cyanoacetate (3.43). To a solution of alcohol **3.41** (42 mg, 0.091 mmol) and DCC (21 mg, 0.10 mmol) dissolved in a 400:1 mixture of DCM:pyridine (3.6 mL) were added cyanoacetic acid (8.5 mg, 0.10 mmol). After 4 h, additional DCC (11 mg, 0.053 mmol) and cyanoacetic acid (4.0 mg, 0.047 mmol) was added to the reaction. After 2 h, the reaction was filtered through a plug of Celite®. The filtrate was diluted with water and extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material showed unreacted starting material and was resubjected to the original reaction conditions and stirred overnight. Following the workup from the first reaction cycle, the crude material showed unreacted starting material and resubjected to the original reaction conditions but with additional DCC (42 mg, 0.20 mmol) and cyanoacetic acid (17 mg, 0.20 mmol) and stirred overnight. Following the reaction workup from the first reaction cycle, the crude material showed full conversion of the starting material. The crude material was purified via silica gel flash chromatograph (4:1

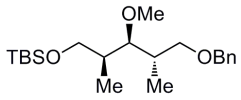
hexanes:EtOAc) to yield 34.0 mg of product as a colorless oil (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.12 (m, 2H), 6.86 – 6.76 (m, 2H), 5.18 (td, *J* = 6.9, 1.9 Hz, 1H), 5.13 – 5.00 (m, 1H), 4.31 (s, 2H), 3.73 (s, 3H), 3.42 – 3.30 (m, 5H), 3.27 (s, 2H), 2.96 (dd, *J* = 9.3, 2.3 Hz, 1H), 2.23 – 2.00 (m, 2H), 1.97 (s, 3H), 1.81 (dd, *J* = 8.3, 5.8 Hz, 2H), 1.77 – 1.62 (m, 6H), 1.54 (dtt, *J* = 9.2, 7.1, 3.5 Hz, 1H), 1.36 (p, *J* = 7.3 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 162.8, 159.1, 130.4, 129.3, 113.7, 113.2, 83.8, 78.0, 74.6, 72.8, 69.7, 68.9, 61.5, 55.2, 43.8, 40.4, 35.6, 34.4, 24.8, 24.5, 21.0, 19.6, 12.8, 12.0, 10.5, 3.4.



3.48

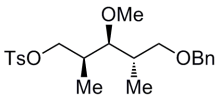
(*2S,3S,4S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-methoxy-2,4-dimethylpentan-1-ol (3.48). To a solution of olefin **3.33** (2.23 g, 8.18 mmol) in DCM (41 mL) and methanol (41 mL) at -78 °C was bubbled ozone until the reaction turned blue. After bubbling oxygen thru the reaction for 15 min, sodium borohydride (0.93 g, 25 mmol) was added the reaction. The reaction was warmed to room temperature and stirred for 3 h. The reaction was diluted with EtOAc and quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (20% EtOAc in hexanes) to yield 1.95 g of product as a colorless oil (86% yield). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 3.71 – 3.59 (m, 2H), 3.55 – 3.43 (m, 5H), 1.98 – 1.78 (m, 2H), 0.90 (s, 9H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.5, 67.2, 65.5, 61.1, 38.5, 37.6, 25.9, 18.2, 14.7, 10.5, -5.4, -5.4. HRMS calc *m/z* $[C_{14}H_{32}O_3Si + Na]^+$: 299.2019, found: 299.2019.



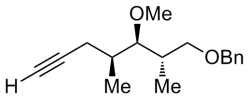
3.49

(((*2S,3S,4S*)-5-(Benzyloxy)-3-methoxy-2,4-dimethylpentyl)oxy)(tert-butyl)dimethylsilane (3.49). To a solution of alcohol **3.48** (0.85 g, 3.1 mmol) in DMF (8.7 mL) at 0 °C was added sodium hydride (60% in mineral oil, 0.23 g, 5.8 mmol). The suspension was stirred at 0 °C for 15 min before addition of benzyl bromide (0.69 mL, 5.8 mmol). The reaction was stirred an addition 2.5 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via Combiflash silica gel flash chromatograph (0% to 2.5% EtOAc in hexanes) to yield 1.02 g of product as a colorless oil (92% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 4.63 – 4.47 (ABq, 2H), 3.62 – 3.45 (m, 4H), 3.39 (s, 3H), 3.28 (dd, *J* = 9.0, 2.8 Hz, 1H), 1.93 (ddt, *J* = 12.9, 6.7, 3.4 Hz, 1H), 1.89 – 1.74 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.3, 127.4, 127.3, 82.0, 73.0, 72.9, 65.6, 60.9, 37.8, 36.8, 25.9, 18.2, 14.8, 9.9, -5.3, -5.4. HRMS calc *m/z* $[C_{21}H_{38}O_3Si + Na]^+$: 389.2482, found: 389.2481.



3.47

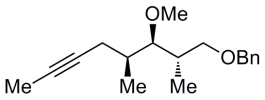
(*2S,3S,4S*)-5-(Benzyloxy)-3-methoxy-2,4-dimethylpentyl 4-Methylbenzenesulfonate (3.47). The product was synthesized using the procedure for the synthesis of tosylate **3.26**. Reaction with ether **3.49** (2.42 g, 6.60 mmol) resulted in 2.52 g of product as a colorless oil (94% yield) following purification via silica gel flash chromatography (15% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.39 – 7.27 (m, 7H), 4.48 (s, 2H), 4.01 (dd, *J* = 9.3, 8.1 Hz, 1H), 3.91 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.46 (h, *J* = 5.1 Hz, 2H), 3.27 (s, 3H), 3.16 (dd, *J* = 8.9, 2.8 Hz, 1H), 2.44 (s, 3H), 2.11 – 1.97 (m, 1H), 1.93 – 1.76 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 138.6, 133.1, 129.8, 128.3, 127.9, 127.5, 127.5, 81.3, 73.1, 72.8, 72.2, 60.9, 36.6, 35.0, 21.6, 14.5, 9.6. HRMS calc *m/z* $[C_{22}H_{30}O_5S + Na]^+$: 429.1706, found: 429.1619.



3.50

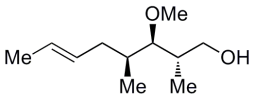
((((*2S,3R,4S*)-3-Methoxy-2,4-dimethylhept-6-yn-1-yl)oxy)methyl)benzene (3.50). The product was synthesized using the procedure for the synthesis of alkyne **3.35**. Reaction with tosylate **3.47** (2.53 g, 6.22 mmol) resulted in 1.39 g of product as a colorless oil (86% yield) following purification via silica gel flash chromatography (4% to 6% ether in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.31 – 7.26 (m, 1H), 4.52 (s, 2H), 3.60 – 3.46 (m, 2H), 3.43 (s, 3H), 3.21 (dd, *J* = 8.6, 3.2 Hz, 1H), 2.25 (qdd, *J* = 16.7, 7.2, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.97 – 1.82 (m, 2H), 0.98 (d, *J* = 6.9 Hz,

3H), 0.94 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.3, 127.5, 127.4, 84.4, 83.6, 73.1, 72.5, 69.3, 61.3, 37.0, 35.1, 23.7, 14.8, 13.2. HRMS calc m/z [$C_{17}H_{24}O_2$ + Na]$^+$: 283.1669, found: 283.1645.



3.46

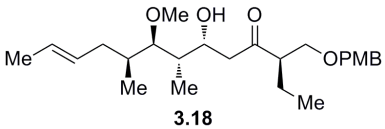
((((*2S,3R,4S*)-3-Methoxy-2,4-dimethyloct-6-yn-1-yl)oxy)methyl)benzene (3.46). To solution of alkyne **3.50** (0.927 g, 3.56 mmol) in THF (36 mL) at -78 °C, was added a solution of LiHMDS (1 M in hexanes, 17.8 mL, 17.8 mmol). After stirring for 2 h at -78 °C, iodomethane (3.3 mL, 53 mmol) was added to the reaction. The reaction was warmed to room temperature and stirred for an additional 2 h. The reaction was quenched with water and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (5% ether in pentane) to yield 0.945 g of product as a colorless oil (97% yield). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[50]



3.51

(*2S,3R,4S,E*)-3-Methoxy-2,4-dimethyloct-6-en-1-ol (3.51). The product was synthesized following a previously reported procedure.[50] To a solution of ammonia (16 mL) and THF (8 mL) at -78 °C was added alkyne **3.46** (0.87 g, 3.2 mmol) dissolved in THF (2 mL). The flask containing the alkyne with rinsed with additional THF (2 mL)

which was added to the reaction; this was repeated two more times. A few pieces of lithium wire were added to the reaction and the reaction was stirred at -78 °C for 20 min before warming to -40 °C. After 1 h, additional lithium wire was added to the reaction. After stirring an additional 2 h at -40 °C, additional lithium wire was added to the reaction. After stirring an additional 3 h at -40 °C, the reaction was warmed to room temperature to evaporate the ammonia. The reaction was quenched with the slow addition of solid NH_4Cl followed by saturated aqueous NH_4Cl. The reaction was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (24% EtOAc in hexanes) to yield 0.569 g of product as a colorless oil (96% yield). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[50]

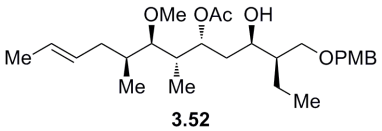


3.18

(*3R,6R,7S,8R,9S,E*)-6-Hydroxy-8-methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-dimethyltridec-11-en-4-one (3.18). The synthesis was adapted from previously reported procedures.[50] A suspension of alcohol **3.51** (105 mg, 0.564 mmol), NMO (78 mg, 0.67 mmol), and powdered 4Å molecular sieves (150 mg) was stirred in DCM (4.5 mL) at 0 °C for 15 min. A solution of TPAP (20. mg, 0.056 mmol) in DCM (0.5 mL) was added to the reaction. After stirring at 0 °C for 40 min, the reaction was diluted with 20% EtOAc in hexanes and filtered through a plug of silica gel. The silica gel plug was rinsed

with 20% acetate in hexanes. The crude aldehyde solution was concentrated using a rotary evaporator and the crude aldehyde was used without further purification.

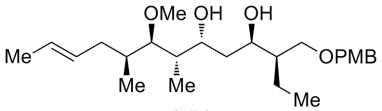
The crude aldehyde was combined with crude silyl enol ethers **3.20** (~1.9 mmol) and dissolved in DCM (5.1 mL) and cooled in a MeOH/*lq* N_2 bath. BF_3•Et_2O (0.53 mL, 4.2 mmol) was added dropwise to the reaction and the reaction was stirred in the MeOH/*lq* N_2 bath for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ solution and warmed to room temperature. The layers were separated and the aqueous phase was extracted three times with DCM and once with EtOAc. The combined organic extracts were washed with brine and dry with Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed by rotary evaporator. The crude material was initially purified via silica gel flash chromatography (15% EtOAc in hexanes) and subsequently purified via Combiflash® silica gel column (5% to 15% EtOAc in hexanes) to yield 141.4 mg of product as a colorless oil (60% yield over 2 steps). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[50]



3.52

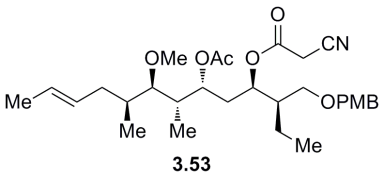
(*3R,4R,6R,7S,8R,9S,E*)-4-Hydroxy-8-methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-dimethyltridec-11-en-6-yl Acetate (3.52). The product was synthesized using the procedure for the synthesis of alcohol **3.41**. Reaction with ketone **3.18** (40.6 mg, 0.0965 mmol) resulted in 39.5 mg of product as a colorless oil (88% yield) following purification via silica gel flash chromatography (25% EtOAc in hexanes). ^1H NMR (400 MHz,

$CDCl_3$) δ 7.24 (d, *J* = 6.3 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.54 – 5.33 (m, 3H), 4.53 – 4.37 (m, 2H), 3.82 (s, 3H), 3.74 (d, *J* = 7.0 Hz, 1H), 3.69 (d, *J* = 10.9 Hz, 1H), 3.59 – 3.46 (m, 2H), 3.40 (s, 3H), 3.31 (s, 1H), 2.85 (d, *J* = 10.3 Hz, 1H), 2.23 – 1.90 (m, 5H), 1.79 – 1.63 (m, 5H), 1.64 – 1.50 (m, 3H), 1.51 – 1.31 (m, 2H), 1.31 – 1.19 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 159.1, 130.5, 130.2, 129.2, 126.4, 113.8, 85.4, 72.9, 71.8, 70.7, 68.7, 65.8, 61.3, 60.4, 55.3, 45.5, 40.3, 38.4, 37.7, 35.8, 31.6, 22.6, 21.2, 19.1, 18.0, 15.3, 14.2, 14.1, 12.4, 12.3, 10.6.



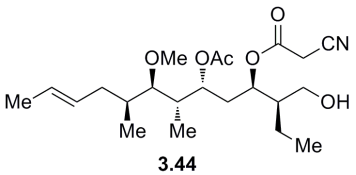
3.54

(*3R,4R,6R,7S,8R,9S,E*)-8-Methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-dimethyltridec-11-ene-4,6-diol (3.54). To a solution of alcohol **3.52** (5.6 mg, 0.012 mmol) in methanol (0.5 mL) was added potassium hydroxide (2.2 mg, 0.039 mmol) and the reaction was stirred at room temperature. After 5 h, the reaction was quenched with saturated aqueous NH_4Cl, and extracted four times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (40% EtOAc in hexanes) to yield 4.7 mg of product as a colorless oil (92% yield). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[50]



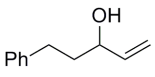
3.53

(*3R,4R,6R,7S,8R,9S,E*)-6-Acetoxy-8-methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-dimethyltridec-11-en-4-yl 2-Cyanoacetate (3.53). To a solution of alcohol **3.54** (83 mg, 0.18 mmol) and DCC (221 mg, 1.07 mmol) dissolved in a 300:2 mixture of DCM:pyridine (7.1 mL) was added cyanoacetic acid (91 mg, 1.1 mmol). After stirring overnight at room temperature, the reaction was filtered through a plug of Celite®. The filtrate was diluted with water and extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified initially via silica gel flash chromatograph (35% ether in hexanes). Impure material was further purified via silica gel flash chromatograph (40% ether in hexanes). The products from the two columns were combined to yield 77.2 mg of product as a colorless oil (81% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.92 – 6.80 (m, 2H), 5.57 – 5.34 (m, 2H), 5.20 (ddd, *J* = 8.1, 5.8, 2.0 Hz, 1H), 5.11 (ddt, *J* = 8.2, 6.8, 3.4 Hz, 1H), 4.37 (s, 2H), 3.79 (s, 3H), 3.49 – 3.35 (m, 7H), 2.81 (dd, *J* = 9.2, 2.3 Hz, 1H), 2.20 – 2.06 (m, 1H), 2.01 (s, 3H), 2.00 – 1.92 (m, 1H), 1.88 – 1.82 (m, 2H), 1.77 (tdd, *J* = 10.4, 8.7, 5.5 Hz, 2H), 1.69 – 1.53 (m, 6H), 1.49 – 1.37 (m, 3H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 171.3, 163.7, 159.8, 131.2, 130.7, 129.8, 128.9, 126.9, 114.2, 85.8, 75.3, 73.3, 70.4, 69.5, 61.6, 55.8, 44.4, 41.0, 38.9, 36.4, 35.1, 25.4, 21.4, 20.3, 18.3, 12.8, 12.3, 10.9.



3.44

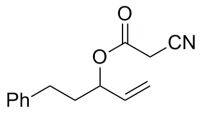
(*3R,4R,6R,7S,8R,9S,E*)-6-Acetoxy-3-(hydroxymethyl)-8-methoxy-7,9-dimethyltridec-11-en-4-yl 2-Cyanoacetate (3.44). To a solution of ester **3.53** (31.3 mg, 0.0589 mmol) in DCM (1 mL) and water (0.09 mL) was added DDQ (33 mg, 0.15 mmol). After stirring 20 min, the reaction was diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with DCM and once with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (40% EtOAc in hexanes) to yield 17.9 mg of product as a colorless oil (74% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.52 – 5.35 (m, 2H), 5.26 (ddd, *J* = 9.4, 4.1, 1.9 Hz, 1H), 5.13 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.71 – 3.57 (m, 1H), 3.52 (d, *J* = 1.8 Hz, 2H), 3.48 – 3.34 (m, 4H), 2.81 (dd, *J* = 9.3, 2.3 Hz, 1H), 2.22 – 2.06 (m, 2H), 2.06 – 1.89 (m, 5H), 1.89 – 1.80 (m, 1H), 1.74 – 1.59 (m, 7H), 1.51 – 1.40 (m, 1H), 1.35 – 1.16 (m, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.85 (d, *J* = 7.1 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 171.5, 164.8, 130.7, 126.9, 113.9, 85.8, 74.6, 70.2, 62.1, 61.6, 46.6, 41.1, 38.9, 36.4, 35.6, 25.5, 21.4, 19.4, 18.3, 12.8, 12.5, 10.9.



3.61

5-Phenylpent-1-en-3-ol (3.61). To a solution of hydrocinnamaldehyde (**3.60**, 3.0 mL, 23 mmol) in ether (27 mL) at 0 °C was added a solution of vinyl magnesium bromide (1 M

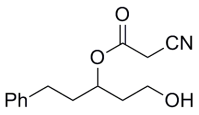
in THF, 27 mL, 27 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The reaction was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (20% EtOAc in hexanes) to yield 2.10 g of product as a colorless oil (56% yield). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[124]



3.62

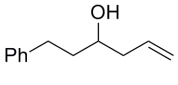
5-Phenylpent-1-en-3-yl 2-Cyanoacetate (3.62). To a solution of alcohol **3.61** (1.03 g, 6.35 mmol) and DCC (1.40 g, 6.79 mmol) dissolved in a 400:1 mixture of DCM:pyridine (250 mL) was added cyanoacetic acid (0.58 g, 6.8 mmol). After stirring overnight at room temperature, the reaction was filtered through a plug of Celite®. The filtrate was diluted with water and extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (20% EtOAc in hexanes) to yield 1.31 g of product as a colorless oil (92% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.24 – 7.13 (m, 3H), 5.81 (ddd, J = 17.3, 10.5, 6.7 Hz, 1H), 5.43 – 5.21 (m, 3H), 3.42 – 3.29 (m, 2H), 2.68 (t, J = 7.8 Hz, 2H), 2.17 – 1.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 140.7, 134.8, 128.5, 128.3, 126.2, 118.7, 112.9, 35.3,

31.3, 24.8.



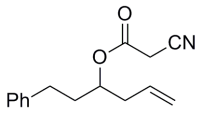
3.59

1-Hydroxy-5-phenylpentan-3-yl 2-Cyanoacetate (3.59). To a solution of ester **3.62** (0.15 g, 0.65 mmol) in THF (6.5 mL) at 0 °C was added a solution of 9-BBN (0.5 M in THF, 4 mL, 2 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C and a solution of NaOH (3 M, 0.54 mL) and solution of hydrogen peroxide (30%, 0.54 mL) was added to the reaction. The reaction was warmed to room temperature. The reaction was poured into a solution of Rochelle salt (10%, 17.5 mL) and glycerine (0.13 mL). The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was initially purified via silica gel flash chromatograph (10% to 20% EtOAc in DCM). Subsequent purifications via silica gel flash chromatograph 2% methanol in chloroform followed by 40% in hexanes) to yield 0.532 g of product as a colorless oil (33% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.35 – 7.24 (m, 2H), 7.24 – 7.15 (m, 3H), 4.51 – 4.23 (m, 2H), 3.82 – 3.65 (m, 1H), 3.46 (s, 1H), 2.86 – 2.60 (m, 2H), 1.99 – 1.84 (m, 1H), 1.84 – 1.65 (m, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 163.9, 142.5, 129.0, 128.9, 126.4, 68.4, 64.7, 39.9, 36.5, 32.4, 25.4.



3.65

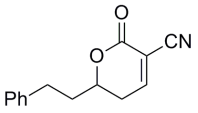
1-Phenylhex-5-en-3-ol (3.65). The product was synthesized following a previously reported procedure.[125] To a solution of hydrocinnamaldehyde (**3.60**, 2.0 mL, 15 mmol) in ether (40 mL) at 0 °C was added a solution of allyl magnesium bromide (1 M in ether, 23 mL, 23 mmol). The reaction was warmed to room temperature over 1 h and then quenched with saturated aqueous NH_4Cl. The reaction was extracted three times with ether. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (20% EtOAc in hexanes) to yield 1.58 g of product as a colorless oil (59% yield). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[125]



3.66

1-Phenylhex-5-en-3-yl 2-Cyanoacetate (3.66). To a solution of alcohol **3.65** (0.40 g, 2.3 mmol) and DCC (0.52 g, 2.5 mmol) dissolved in a 400:1 mixture of DCM:pyridine (91 mL) at 0 °C was added cyanoacetic acid (0.21 g, 2.5 mmol). The reaction was warmed to room temperature and stirred for 4 h. The reaction was filtered through a plug of Celite®. The filtrate was diluted with water and extracted three times with DCM. The combined organic layers were washed twice with water and once with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (5:1 hexanes:EtOAc) to yield 0.41 g of product as a

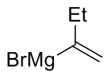
colorless oil (74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.24 – 7.13 (m, 3H), 5.73 (ddt, *J* = 17.2, 9.4, 7.1 Hz, 1H), 5.18 – 5.08 (m, 2H), 5.05 (p, *J* = 6.2 Hz, 1H), 3.44 – 3.21 (ABq, 2H), 2.67 (t, *J* = 7.8 Hz, 2H), 2.48 – 2.31 (m, 2H), 2.05 – 1.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 140.9, 132.6, 128.5, 128.3, 126.1, 118.7, 113.0, 76.2, 38.6, 34.8, 31.7, 24.7.



3.64

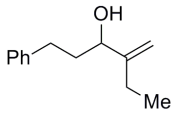
2-Oxo-6-phenethyl-5,6-dihydro-2*H*-pyran-3-carbonitrile (3.64). To a solution of ester **3.66** (100. mg, 0.411 mmol) in DCM (1.9 mL) and methanol (0.4 mL) at -78 °C, was bubbled ozone until the reaction turned blue. After the reaction was purged with nitrogen, dimethyl sulfide (0.12 mL, 1.6 mmol) was added to the reaction. After stirring at -78 °C for 10 min, pH 7 phosphate buffer (3 mL) was added to the reaction. The reaction was warmed to room temperature and stirred for 5 h. The mixture was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (3% methanol in chloroform) to yield 70.8 mg of product as a beige solid (76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (t, *J* = 4.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.15 (m, 3H), 4.58 – 4.38 (m, 1H), 2.89 (ddd, *J* = 14.3, 9.0, 5.5 Hz, 1H), 2.79 (dt, *J* = 14.0, 8.0 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.18 (dtd, *J* = 14.1, 8.5, 5.5 Hz, 1H), 1.99 (dddd, *J* = 14.1, 12.2, 7.6, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 157.4, 140.0, 128.7, 128.4, 126.4, 113.2, 110.6, 77.0, 36.1, 30.6, 30.2. mp: 98.7 –

99.8 °C.



3.67

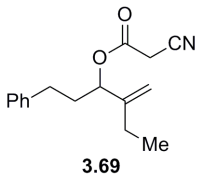
But-1-en-2-ylmagnesium Bromide (3.67). To a suspension of magnesium turnings (0.48 g, 20 mmol) in THF (9.2 mL) was added 2-bromo-1-butene (1.35 g, 10.0 mmol) followed by 1,2-dibromobutane (0.04 mL, 0.5 mmol). The reaction exotherms to reflux, and was stirred at room temperature overnight. The Grignard solution was titrated with 2-((2-phenylhydrazono)methyl)phenol.[126]



3.68

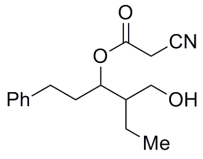
4-Methylene-1-phenylhexan-3-ol (3.68). To a solution of hydrocinnamaldehyde (**3.60**, 0.70 mL, 5.4 mmol) in ether (6.4 mL) at 0 °C was added a solution of Grignard **3.67** (0.74 M in THF, 8.0 mL, 5.9 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The reaction was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (8:1 hexanes:EtOAc) to yield 0.526 g of product as a colorless oil (52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H), 5.08 – 5.02 (m, 1H), 4.88 (d, *J* = 1.5 Hz, 1H), 4.12 (dd, *J* = 7.6, 5.1 Hz, 1H), 2.70 (dddd, *J* = 41.4, 13.9, 9.8, 6.4 Hz, 2H), 2.20 – 1.96 (m, 2H), 1.96 – 1.78 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 142.0, 128.4, 128.4, 125.8, 108.7, 74.9, 37.1,

32.0, 24.0, 12.3.



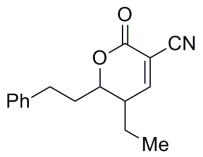
3.69

4-Methylene-1-phenylhexan-3-yl 2-Cyanoacetate (3.69). The product was synthesized using the procedure for the synthesis of ester **3.62**. Reaction with alcohol **3.68** (0.40 g, 2.1 mmol) resulted in 0.53 g of product as a colorless oil (98% yield) following purification via silica gel flash chromatography (8:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.11 (m, 3H), 5.30 (dd, *J* = 7.8, 5.3 Hz, 1H), 5.08 (q, *J* = 1.1 Hz, 1H), 4.98 (q, *J* = 1.5 Hz, 1H), 3.43 – 3.27 (m, 2H), 2.70 – 2.57 (m, 2H), 2.14 – 1.93 (m, 4H), 1.08 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 147.6, 140.8, 128.5, 128.3, 126.1, 111.7, 79.8, 34.4, 31.8, 24.8, 24.3, 11.9.



3.70

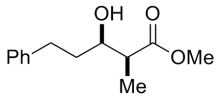
4-(Hydroxymethyl)-1-phenylhexan-3-yl 2-Cyanoacetate (3.70). The product was synthesized using the procedure for the synthesis of alcohol **3.59**. Reaction with ester **3.69** (0.585 g, 2.27 mmol) resulted in 0.404 g of product as a colorless oil (64% yield) following purification via silica gel flash chromatography (7:3 hexanes:EtOAc). Main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.19 (dd, *J* = 12.3, 7.1 Hz, 3H), 5.22 – 5.11 (m, 1H), 3.78 – 3.59 (m, 2H), 3.51 – 3.37 (m, 1H), 3.37 – 3.09 (m, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 2.11 – 1.98 (m, 2H), 1.77 – 1.56 (m, 3H), 1.52 – 1.34 (m, 2H), 0.95 (td, *J* = 7.4, 5.4 Hz, 3H).



3.71

5-Ethyl-2-oxo-6-phenethyl-5,6-dihydro-2*H*-pyran-3-carbonitrile (3.71). To a solution of alcohol **3.65** (59 mg, 0.21 mmol) and 1,3,5-trimethoxybenene (12.0 mg, 0.713 mmol) in DCM (0.9 mL) was added a solution of Dess-Martin Periodinane (0.3 M in DCM, 1.4 mL, 0.42 mmol). After stirring at room temperature for 30 min, the reaction was washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted three times with DCM. The combined organic layers were washed twice with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$, twice with saturated aqueous $NaHCO_3$, and once with brine. The combined organic layers were dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The ^1H NMR spectra of the crude material showed traces of Dess-Martin Periodinane byproducts. The crude material was dissolved in DCM and wash twice with a 1:1 mixture of saturated aqueous $NaHCO_3$, and once with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. One third of the crude material was dissolved in 0.5 mL DCM and stirred overnight with 30 mg basic Al_2O_3. The suspension was filtered and volatile materials were removed using a rotary evaporator. The ^1H NMR spectra of the crude material showed 40% cyclization product based on the 1,3,5-trimethoxybenzene standard. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 3.4 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.25 – 7.16 (m,

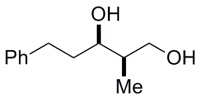
3H), 4.30 (td, *J* = 8.4, 3.7 Hz, 1H), 3.00 – 2.88 (m, 1H), 2.86 – 2.70 (m, 1H), 2.51 (tdd, *J* = 8.2, 4.9, 3.4 Hz, 1H), 2.19 – 1.93 (m, 2H), 1.81 – 1.63 (m, 1H), 1.54 – 1.44 (m, 1H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 158.2, 140.2, 128.7, 128.4, 126.4, 113.2, 110.0, 80.6, 40.5, 34.7, 30.8, 23.3, 10.5.



3.75

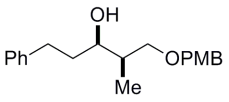
Methyl (*2,3-syn*)-3-Hydroxy-2-methyl-5-phenylpentanoate (3.75). To a solution of methyl propionate (**3.74,** 0.51 mL, 5.3 mmol) in DCM (42 mL) at 0 °C was added DIPEA (5.3 mL, 30.4 mmol) followed by the dropwise addition of a solution of Bu_2BOTf (1 M in DCM, 10.5 mL, 10.5 mmol). After stirring at 0 °C for 30 min, the reaction was cooled to -78 °C followed by the dropwise addition of hydrocinnemaldehyde (**3.60**, 1.0 mL, 7.6 mmol). The reaction was stirred at -78 °C for 1 h, followed by stirring at 0 °C for an additional 1 h. The reaction was quenched with pH 7 phosphate buffer (20 mL) and warmed to room temperature. The mixture was poured into a mixture of methanol (210 mL) and 30% hydrogen peroxide (10 mL) and stirred overnight. The mixture was concentrated via rotary evaporator and the residual mixture was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (4:1 hexanes:EtOAc). The impure product for further purified via silica gel flash chromatograph (4:1 hexanes:EtOAc) to yield 0.984 g of product as a colorless oil (84% yield). The resonances in the ^{1}H NMR and ^{13}C spectrum of the

product matched previously reported chemical shifts for the scalemic product.[127]



3.76

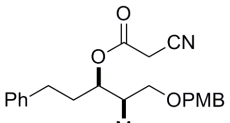
(*2,3-syn*)-2-Methyl-5-phenylpentane-1,3-diol (3.76). To a suspension of lithium aluminum hydride (0.88 g, 23 mmol) in ether (50 mL) at 0 °C was cannula transferred dropwise a solution of ester **3.75** (1.29 g, 5.80 mmol) in ether (17 mL). The reaction was warmed to room temperature stirred for 2.5 h before cooling to 0 °C. The reaction was quenched with the addition of water (0.9 mL), 15% sodium hydroxide (0.9 mL), followed by water (2.7 mL). The reaction was allowed to warm to room temperature and was stirred for 20 min. The suspension was filtered through Celite®, and the filtrate was concentrated using a rotary evaporator. The residue was diluted with DCM and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via Combiflash® silica gel flash chromatograph (30% to 50% EtOAc in hexanes) to yield 1.03 g of product as a colorless oil (92% yield). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[128]



3.77

(*2,3-syn*)-1-((4-Methoxybenzyl)oxy)-2-methyl-5-phenylpentan-3-ol (3.77). To a suspension of sodium hydride (60% in mineral oil, 220 mg, 5.5 mmol) in DMF (18 mL) was added a solution of diol **3.76** (0.267 g, 1.4 mmol) in DMF (12 mL). The reaction was stirred at room temperature for 45 min before cooling to 0 °C. PMBCl (0.19 mL, 1.4

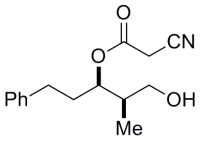
mmol) was added dropwise and the reaction was stirred at 0 °C for 5 h. The reaction was quenched with saturated aqueous NH_4Cl, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed twice with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material contained residual DMF. The crude material was dissolved in ether and washed 5 times with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (25% EtOAc in hexanes) to yield 0.293 g of product as a colorless oil (68% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 – 7.10 (m, 6H), 6.96 – 6.81 (m, 2H), 4.48 – 4.24 (m, 2H), 3.74 (s, 3H), 3.49 (td, J = 6.4, 3.6 Hz, 1H), 3.43 – 3.36 (m, 1H), 3.20 (dd, J = 9.1, 6.6 Hz, 1H), 2.70 (dt, J = 14.7, 7.7 Hz, 1H), 2.60 – 2.51 (m, 1H), 1.70 (qd, J = 6.7, 3.7 Hz, 1H), 1.65 – 1.53 (m, 2H), 1.09 (t, J = 7.0 Hz, 1H), 0.82 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.6, 142.5, 130.6, 129.0, 128.3, 128.2, 125.5, 113.6, 72.5, 71.7, 69.5, 55.0, 38.3, 36.5, 32.0, 11.3.



3.78

(*2,3-syn*)-1-((4-Methoxybenzyl)oxy)-2-methyl-5-phenylpentan-3-yl 2-Cyanoacetate (3.78). To a solution of alcohol **3.77** (0.159 g, 0.506 mmol) and DCC (0.42 g, 2.0 mmol) dissolved in a 100:1 mixture of DCM:pyridine (20 mL) at 0 °C was added cyanoacetic acid (0.172 g, 2.02 mmol). The reaction was warmed to room temperature and stirred

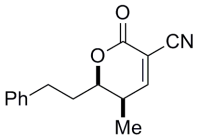
overnight. The reaction was filtered through a plug of Celite®. The filtrate was diluted with water and extracted four times with DCM. The combined organic layers were washed twice with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (25% EtOAc in hexanes) to yield 0.167 g of product as a colorless oil (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 5H), 7.18 – 7.11 (m, 2H), 6.93 – 6.85 (m, 2H), 5.24 (dt, *J* = 8.4, 4.1 Hz, 1H), 4.45 – 4.30 (m, 2H), 3.81 (s, 3H), 3.38 – 3.25 (m, 2H), 3.24 – 3.10 (m, 2H), 2.63 (ddd, *J* = 8.9, 6.8, 1.9 Hz, 2H), 2.12 – 1.96 (m, 2H), 1.86 (dddd, *J* = 14.0, 8.9, 7.1, 4.5 Hz, 1H), 0.97 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 159.2, 141.1, 130.2, 129.5, 128.5, 128.3, 126.1, 113.8, 113.1, 77.7, 72.9, 71.8, 55.3, 37.0, 33.2, 32.2, 24.6, 11.3.



3.73

(*2,3-syn*)-1-Hydroxy-2-methyl-5-phenylpentan-3-yl 2-Cyanoacetate (3.73). To a solution of ester **3.78** (0.167 g, 0.437 mmol) in DCM (2.3 mL) and water (0.23 mL) was added DDQ (0.25 g, 1.1 mmol). After stirring for 1 h, the reaction was diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with DCM and once with EtOAc. The combined organic layers were washed with brine and the resulting emulsion was filtered through a plug of Celite®. The layers were separated and the organic layer was dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials

were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (40% EtOAc in hexanes) to yield 0.0805 mg of product as a colorless oil (70% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.36 – 7.26 (m, 2H), 7.25 – 7.15 (m, 3H), 5.22 (dt, *J* = 9.2, 3.6 Hz, 1H), 3.52 – 3.28 (m, 4H), 2.66 (t, *J* = 7.8 Hz, 2H), 2.18 – 1.99 (m, 1H), 2.01 – 1.75 (m, 3H), 1.15 (t, *J* = 7.0 Hz, 1H), 0.90 (d, *J* = 7.0 Hz, 3H).

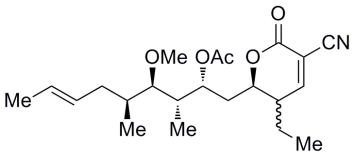


3.79

(*5,6-syn*)-5-Methyl-2-oxo-6-phenethyl-5,6-dihydro-2*H*-pyran-3-carbonitrile (3.79). To a solution of alcohol **3.73** (23.6 mg, 0.0903 mmol) in DCM (0.45 mL) was added a solution of Dess-Martin Periodinane (0.3 M in DCM, 0.60 mL, 0.18 mmol). After stirring at room temperature for 2 h, the reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ and stirred at room temperature for 15 min. The mixture was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator to yield 21 mg of crude aldehyde product.

To a suspension of sodium hydride (60% in mineral oil, 3.4 mg, 0.085 mmol) in THF (0.4 mL) at -20 °C, was added dropwise a solution of the crude aldehyde in THF (0.2 mL). The vial containing the crude aldehyde was rinsed with additional THF (0.2 mL) which was added to the reaction. The reaction was stirred at -20 °C for 30 min before quenching with saturated aqueous NH_4Cl. The mixture was extract four times

with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The ^1H NMR spectra of the crude material showed a 30:1 mixture of lactone **3.39** to α,β-unsaturated aldehyde **3.80**. The crude material was purified via silica gel flash chromatograph (30% EtOAc in hexanes) to yield 7.7 mg of product as a colorless oil (35% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 6.3 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.13 (m, 3H), 4.44 (dt, *J* = 9.4, 3.7 Hz, 1H), 2.92 (ddd, *J* = 14.2, 9.0, 5.3 Hz, 1H), 2.74 (dt, *J* = 13.8, 8.1 Hz, 1H), 2.58 (pd, *J* = 7.0, 3.3 Hz, 1H), 2.18 (ddt, *J* = 14.3, 9.1, 4.4 Hz, 1H), 1.83 (dddd, *J* = 13.9, 8.8, 7.6, 4.0 Hz, 1H), 1.15 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 158.8, 140.1, 128.7, 128.4, 126.5, 113.2, 109.6, 79.1, 33.2, 32.8, 31.0, 10.8.



3.55

(*2R,3S,4R,5S,E*)-1-((*2R*)-5-Cyano-3-ethyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-4-methoxy-3,5-dimethylnon-7-en-2-yl Acetate (3.55)... To a solution of alcohol **3.44** (11.2 mg, 0.0272 mmol) in DCM (0.4 mL) was added a solution of Dess-Martin Periodinane (0.3 M in DCM, 0.18 mL, 0.054 mmol). After stirring at room temperature for 1.5 h, the reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ and stirred at room temperature for 15 min. The mixture was extracted 5 times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and

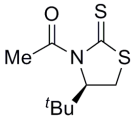
volatile materials were removed using a rotary evaporator to yield crude aldehyde product.

To a suspension of sodium hydride (60% in mineral oil, 1.3 mg, 0.033 mmol) in THF (0.4 mL) at -20 °C, was added dropwise a solution of crude aldehyde in THF (0.2 mL). The vial containing the crude aldehyde was rinsed with additional THF (0.2 mL) which was added to the reaction. The reaction was stirred at -20 °C for 45 min before quenching with saturated aqueous NH_4Cl. The mixture was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The ^1H NMR spectra of the crude material showed lactone product **3.55** as a single isomer. The crude material was purified via silica gel flash chromatograph (10% to 30% EtOAc in hexanes) to yield 5.3 mg of product as a mixture of isomers (50% yield).

Major Isomer: ^1H NMR (400 MHz, CD_2Cl_2) δ 7.76 (d, *J* = 6.3 Hz, 1H), 5.57 – 5.35 (m, 2H), 5.31 – 5.23 (m, 1H), 4.60 – 4.48 (m, 1H), 3.37 (d, *J* = 1.0 Hz, 3H), 2.87 (dd, *J* = 9.3, 2.3 Hz, 1H), 2.55 – 2.47 (m, 1H), 2.20 – 2.09 (m, 1H), 2.07 – 1.93 (m, 5H), 1.93 – 1.76 (m, 2H), 1.76 – 1.45 (m, 6H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.91 – 0.85 (m, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 171.0, 163.6, 159.1, 130.5, 126.8, 113.9, 110.2, 85.5, 78.2, 70.4, 61.4, 61.4, 40.7, 40.3, 39.8, 38.6, 36.2, 35.1, 21.3, 20.8, 18.1, 12.6, 11.1, 10.6.

Minor Isomer:^1H NMR (400 MHz, CD_2Cl_2) δ 7.56 (d, *J* = 3.5 Hz, 1H), 5.57 – 5.35 (m, 2H), 5.31 – 5.23 (m, 1H), 4.41 (td, *J* = 8.2, 3.5 Hz, 1H), 3.37 (d, *J* = 1.0 Hz, 3H), 2.87

(dd, *J* = 9.3, 2.3 Hz, 1H), 2.58 (dd, *J* = 7.7, 3.6 Hz, 1H), 2.20 – 2.09 (m, 1H), 2.07 – 1.93 (m, 5H), 1.93 – 1.76 (m, 2H), 1.76 – 1.45 (m, 6H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.91 – 0.85 (m, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

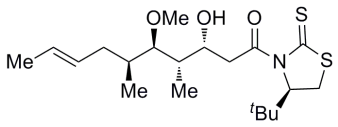


3.97

(*R*)-1-(4-(*tert*-Butyl)-2-thioxothiazolidin-3-yl)ethan-1-one (3.97). The product was synthesized following a previously reported procedure for the corresponding (*S*)-enantiomer.[71] To a suspension of sodium borohydride (1.04 g, 27.4 mmol) in THF (24 mL) was added D-*tert*-leucine (1.2 g, 9.2 mmol); the suspension was cooled to 0 °C. A solution of iodine (2.8 g, 11 mmol) in THF (7.2 mL) was added over 20 min via addition funnel. After the evolution of gas stopped, the reaction was heated to reflux overnight. The reaction was cooled to room temperature and methanol was slowly added until the reaction became clear. After stirring for 40 min at room temperature, volatile materials were removed using a rotary evaporator. The crude material was dissolved in 20% aqueous KOH (19 mL) and stirred for 4 h. Carbon disulfide (4.4 mL, 73 mmol) was added to the solution and the reaction was heated to reflux for 2.5 days. The reaction was cooled to room temperature and the mixture was extracted four times with DCM. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (20% to 25% EtOAc in hexanes) to yield 0.822 g of (*R*)-4-(*tert*-butyl)thiazolidine-2-thione as a white solid (51% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s,

1H), 4.02 (t, J = 8.7 Hz, 1H), 3.39 (qd, J = 11.2, 8.7 Hz, 2H), 0.99 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 73.5, 34.5, 34.3, 25.8. HRMS calc m/z $[C_7H_{13}NS_2 + Na]^+$: 198.0382, found: 198.0395. mp: 138.9 – 140.0 °C.

To a solution of (*R*)-4-(*tert*-butyl)thiazolidine-2-thione (0.50 g, 2.9 mmol) in THF (12.5 mL) at -78 °C was added dropwise a solution of *n*-butyllithium (2.5 M in hexanes, 1.3 mL, 3.1 mmol). After stirring at -78 °C for 30 min, acetyl chloride (0.22 mL, 3.1 mmol) was added dropwise to the reaction. The reaction was stirred at -78 °C for 1 h before warming to room temperature and stirred an additional 30 min. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted four times the DCM. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (10% EtOAc in hexanes) to yield 0.495 g of product as a yellow solid (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (d, J = 8.4 Hz, 1H), 3.53 (dd, J = 11.8, 8.4 Hz, 1H), 3.10 (d, J = 11.7 Hz, 1H), 2.78 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 170.3, 72.0, 38.0, 30.4, 26.8, 26.7. $[\alpha]_D$ = -556.52 (c = 0.229, $CHCl_3$). HRMS calc m/z $[C_9H_{15}NOS_2 + Na]^+$: 240.0487, found: 240.0474. mp: 33.9-35.7 °C.



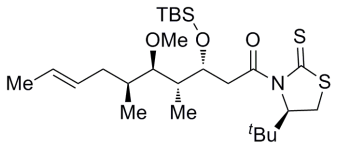
3.98

(*3R,4S,5R,6S,E*)-1-((*R*)-4-(*tert*-Butyl)-2-thioxothiazolidin-3-yl)-3-hydroxy-5-methoxy-4,6-dimethyldec-8-en-1-one (3.98). A suspension of alcohol **3.51** (162 mg, 0.870 mmol), NMO (122 mg, 1.04 mmol), and powdered 4Å molecular sieves (243 mg)

was stirred in DCM (6 mL) at 0 °C for 15 min. A solution of TPAP (31 mg, 0.087 mmol) in DCM (2 mL) was added to the reaction. After stirring 20 min at 0 °C, the reaction was diluted with 40% ethyl acetate in hexanes and filtered through a plug of silica gel. The silica gel plug was rinsed with 40% acetate in hexanes. The crude aldehyde solution was concentrated using a rotary evaporator and the crude aldehyde was used without further purification.

To a solution of thiazolidinethione **3.97** (246 mg, 1.13 mmol) in DCM (3.6 mL) at room temperature was added dichlorophenylborane (0.15 mL, 1.1 mmol). After stirring for 20 min, (+)-sparteine (0.52 mL, 2.3 mmol) was added to the reaction and the reaction was stirred for 30 min before cooling to -78 °C. The crude aldehyde was dissolved in DCM (0.2 mL) and added to the reaction dropwise. The vial containing the aldehyde was rinsed with additional DCM (0.2 mL) which was added to the reaction dropwise. The reaction was stirred at -78 °C for 5 h before warming to room temperature over 2 h and stirred at room temperature for 30 min. The reaction was diluted with hexanes (6 mL) and quenched with 30% hydrogen peroxide (3 mL) and stirred vigorously for 3 min. The reaction was diluted with 4:1 hexanes:DCM (200 mL). The layers were separated and the organic layer was washed with water followed by brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (15% ethyl acetate in hexanes) to yield 244 mg of product as a yellow oil (70% over 2 steps). ^{1}H NMR (400 MHz, C_6D_6) δ 5.56 – 5.34 (m, 2H), 5.02 (d, J = 8.2 Hz, 1H), 4.70 (ddd, J = 8.9, 2.9 Hz, 1H), 3.81 (dd, J = 16.9, 9.8 Hz, 1H), 3.39 (s, 3H),

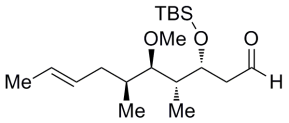
3.37 (d, *J* = 3.8 Hz, 1H), 3.25 – 3.12 (m, 2H), 2.55 (dd, *J* = 11.9, 8.3 Hz, 1H), 2.30 – 2.16 (m, 1H), 2.06 (d, *J* = 11.6 Hz, 2H), 1.83 – 1.65 (m, 2H), 1.62 (d, *J* = 4.3 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.76 (s, 9H). ^{13}C NMR (100 MHz, C_6D_6) δ 205.4, 173.2, 130.7, 126.5, 86.8, 72.3, 67.8, 61.3, 44.0, 40.7, 38.4, 37.9, 36.3, 29.9, 26.8, 18.2, 13.4, 10.9. HRMS calc *m*/*z* $[C_{20}H_{35}NO_3S_2 + Na]^+$: 424.1951, found: 424.1928.



3.99

(*3R,4R,5R,6S,E*)-1-((*R*)-4-(*tert*-Butyl)-2-thioxothiazolidin-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-4,6-dimethyldec-8-en-1-one (3.99). To a solution of alcohol **3.98** (0.68 g, 1.7 mmol) and 2,6-lutidine (0.40 mL, 3.4 mmol) in DCM (17 mL) at 0 °C was added TBSOTf (0.58 mL, 2.5 mmol) dropwise. The reaction was warmed to room temperature and stirred for 45 min before quenching with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted four times with DCM. The combined organic layers were washed with brine and dried with Na_2SO_4. The suspension was filter and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (7% ethyl acetate in hexanes) to yield 0.78 g of product as a yellow oil (89% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 5.54 – 5.31 (m, 2H), 5.09 – 5.01 (m, 1H), 4.99 (d, *J* = 8.1 Hz, 1H), 3.82 (dd, *J* = 16.3, 5.0 Hz, 1H), 3.64 (dd, *J* = 16.3, 7.6 Hz, 1H), 3.49 (s, 3H), 3.31 (dd, *J* = 9.6, 1.8 Hz, 1H), 2.52 (dd, *J* = 11.8, 8.2 Hz, 1H), 2.37 – 2.18 (m, 1H), 2.17 – 2.09 (m, 1H), 2.05 (d, *J* = 11.8 Hz, 1H), 1.94 – 1.80 (m, 1H), 1.80 – 1.68 (m, 1H), 1.64 (d, *J* = 3.8 Hz, 3H), 1.02 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.80 (s, 9H),

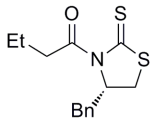
0.27 (s, 3H), 0.25 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 205.5, 170.6, 131.1, 126.4, 84.2, 72.2, 69.5, 61.0, 44.3, 42.2, 38.8, 37.8, 36.2, 30.1, 26.9, 26.3, 18.7, 18.2, 13.2, 10.5, -3.0, -4.1. HRMS calc *m/z* $[C_{26}H_{49}NO_3S_2Si + Na]^+$: 538.2815, found: 538.2816.



3.100

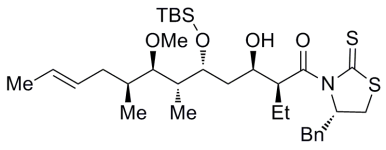
(*3R,4R,5R,6S,E*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-methoxy-4,6-dimethyldec-8-enal (3.100). To a solution of amide **3.99** (280 mg, 0.55 mmol) in DCM (6.1 mL) at -78 °C was added DIBAL-H (1 M in hexanes, 1.1 mL, 1.1 mmol) dropwise. The reaction was determined to be complete after the reaction turned from yellow to clean upon addition of DIBAL-H. The reaction was quenched with saturated aqueous Rochelle salt and diluted with DCM and warmed to room temperature. The slurry was stirred at room temperature for 1.5 h. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (5% acetone in hexanes) to yield 161 mg of product as a colorless oil (85% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 9.47 – 9.40 (m, 1H), 5.53 – 5.31 (m, 2H), 4.67 (td, *J* = 6.1, 1.9 Hz, 1H), 3.38 (s, 3H), 3.17 (dd, *J* = 9.3, 1.9 Hz, 1H), 2.35 (ddd, *J* = 16.4, 6.6, 2.2 Hz, 1H), 2.22 (dt, *J* = 13.1, 6.7 Hz, 1H), 2.16 – 1.95 (m, 2H), 1.74 – 1.55 (m, 4H), 1.51 (ddd, *J* = 9.1, 7.0, 2.0 Hz, 1H), 1.00 – 0.89 (m, 12H), 0.72 (d, *J* = 7.0 Hz, 3H), 0.13 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 199.6, 130.9, 126.6, 84.0,

67.2, 60.6, 51.2, 42.9, 38.8, 36.1, 26.2, 18.5, 18.2, 13.3, 10.5, -3.6, -4.3. HRMS calc *m/z* $[C_{19}H_{38}O_3Si + Na]^+$: 365.2482, found: 365.2446.



3.93

(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)butan-1-one (3.93). The product was synthesized following a previously reported procedure.[99] To a solution of (*S*)-4-benzylthiazolidine-2-thione (0.15 g, 0.72 mmol) and triethylamine (0.11 mL, 0.79 mmol) in DCM (1.1 mL) at 0 °C was added dropwise a solution of butyryl chloride (0.078 mL, 0.75 mmol) dissolved in DCM (0.3 mL) over 2 min. The vial containing the butyryl chloride solution was rinsed with additional DCM (0.3 mL) which was added to the reaction. The reaction was warmed to room temperature and stirred for 4.5 h. The reaction was then quenched with water and the organic layer was separated from the aqueous phase. The aqueous phase was extracted three times with DCM. The combined organic layers was washed with brine and dried with anhydrous Na_2SO_4. The suspension was filter and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (7% acetone in hexanes) to yield 0.169 g of product as a yellow solid (84% yield). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[99]

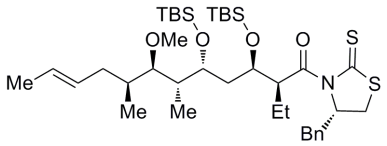


3.101

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-

butyldimethylsilyl)oxy)-2-ethyl-3-hydroxy-7-methoxy-6,8-dimethyldodec-10-en-1-one (3.101). Thiazolidinethione **3.93** (48.4 mg, 0.173 mmol) was dissolved in DCM (0.7 mL) and cooled to 0 °C. Titanium chloride (0.17 mL, 0.17 mmol) was added to the reaction dropwise and the reaction was stirred for 20 min at 0 °C. Diisopropylethylamine (30 μL, 0.17 mmol) was added to the reaction dropwise and the reaction was stirred for an additional 20 min at 0 °C before adding NMP (17 μL, 0.17 mmol) dropwise to the reaction. The reaction was stirred for an additional 20 min at 0 °C before cooling to -78 °C. Aldehyde **3.100** (17.2 mg, 0.0502 mmol) was dissolved in DCM (0.2 mL) and added dropwise to the reaction at -78 °C. The vial containing the aldehyde solution was rinsed with additional DCM (0.2 mL) which was added to the reaction dropwise. The reaction was stirred at -78 °C for 3 h before warmed to -50 °C and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (7:1 hexanes:EtOAc) to yield 23.7 mg of product as a yellow oil (76% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.10 – 7.02 (m, 3H), 7.02 – 6.94 (m, 2H), 5.54 – 5.37 (m, 2H), 5.17 (dd, *J* = 8.9, 4.5 Hz, 1H), 5.11 (ddt, *J* = 10.6, 6.9, 3.4 Hz, 1H), 4.34 (td, *J* = 5.6, 2.8 Hz, 1H), 4.26 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.44 (s, 3H), 3.25 (dd, *J* = 8.6, 2.1 Hz, 1H), 3.10 (dd, *J* = 13.2, 3.7 Hz, 1H), 2.71 (dd, *J* = 13.2, 10.7 Hz, 1H), 2.62 (d, *J* = 3.5 Hz, 1H), 2.55 – 2.45 (m, 1H), 2.36 – 2.21 (m, 1H), 2.22 – 1.99 (m, 4H), 1.98 – 1.82 (m, 2H), 1.82 – 1.68

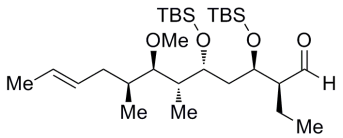
(m, 2H), 1.65 (d, J = 4.1 Hz, 3H), 1.10 (t, J = 7.4 Hz, 3H), 1.02 (s, 9H), 1.02 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.23 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.0, 176.4, 137.0, 130.9, 129.6, 128.9, 127.2, 126.6, 84.6, 71.7, 70.6, 69.4, 60.4, 50.9, 41.7, 40.8, 39.0, 36.9, 36.1, 31.4, 26.3, 20.7, 18.6, 18.2, 13.7, 12.1, 11.4, -3.5, -3.9. HRMS calc m/z $[C_{33}H_{55}NO_4S_2Si + Na]^+$: 644.3234, found: 644.3013.



3.102

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-en-1-one (3.102). To a solution of alcohol **3.101** (0.67 g, 1.1 mmol) and 2,6-lutidine (0.25 mL, 2.2 mmol) in DCM (22 mL) at 0 °C was added TBSOTf (0.37 mL, 1.6 mmol) dropwise. The reaction was removed from the ice bath and stirred at room temperature. After 45 min, TLC analysis of the reactions showed incomplete conversion. The reaction was cooled to 0 °C, and 2,6-lutidine (0.25 mL, 2.2 mmol) followed by TBSOTf (0.37 mL, 1.6 mmol) was added to the reaction. The reaction was removed from the ice bath and stirred at room temperature. After stirring for 20 min, the reaction was quenched with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4% EtOAc in hexanes) to yield 0.751 g of product as a yellow oil (95% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.13 – 6.98 (m, 5H), 5.44 (dt, J = 5.2, 3.5 Hz,

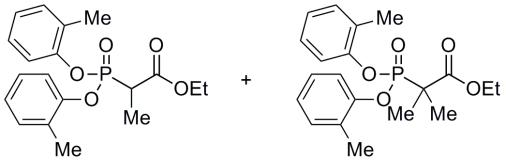
2H), 5.15 (dtd, *J* = 19.7, 7.0, 3.6 Hz, 2H), 4.39 (dd, *J* = 9.3, 4.3 Hz, 1H), 4.22 (dt, *J* = 7.4, 4.5 Hz, 1H), 3.53 (s, 3H), 3.33 (dd, *J* = 9.7, 1.6 Hz, 1H), 3.21 (dd, *J* = 13.1, 3.5 Hz, 1H), 2.88 – 2.73 (m, 2H), 2.40 – 2.21 (m, 3H), 2.22 – 2.06 (m, 2H), 1.95 (dp, *J* = 14.0, 7.1 Hz, 1H), 1.89 – 1.69 (m, 2H), 1.73 – 1.55 (m, 3H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.04 (s, 9H), 1.03 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.30 (s, 3H), 0.28 (s, 3H), 0.21 (s, 6H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 201.3, 176.0, 137.2, 131.1, 129.7, 129.0, 128.5, 127.2, 126.4, 84.1, 71.5, 69.9, 69.7, 61.1, 51.3, 42.9, 41.4, 38.9, 36.7, 36.2, 31.5, 26.3, 26.1, 22.0, 18.7, 18.3, 18.2, 13.2, 12.4, 10.1, -2.5, -2.8, -3.8, -4.1. HRMS calc *m/z* $[C_{38}H_{72}NO_4S_2Si_2 + Na]^+$: 758.4157, found: 758.4145.



3.103

(*2S,3R,5R,6R,7R,8S,E*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-enal (3.103). To a solution of thiazolidinethione **3.102** (0.215 g, 0.292 mmol) in DCM (7.3 mL) at -78 °C was added DIBAL-H (1 M in toluene, 0.58 mL, 0.58 mmol) dropwise. The reaction was determined to be complete after the reaction turned from yellow to clear upon addition of DIBAL-H. The reaction was quenched with saturated aqueous Rochelle salt and diluted with DCM and warmed to room temperature. The slurry was stirred at room temperature for 1.5 h. The layers were separated and the aqueous phase was extracted four times with DCM. The combined organic layers were washed with brine and dried the Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4% EtOAc in hexanes) to yield 0.143 g of

product as a colorless oil (93% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 9.71 (d, *J* = 1.3 Hz, 1H), 5.54 – 5.33 (m, 2H), 4.28 (td, *J* = 7.2, 2.6 Hz, 1H), 4.16 (t, *J* = 7.2 Hz, 1H), 3.41 (s, 3H), 3.26 (dd, *J* = 9.7, 1.7 Hz, 1H), 2.38 – 2.16 (m, 2H), 2.17 – 2.04 (m, 1H), 1.97 (h, *J* = 6.8 Hz, 3H), 1.79 – 1.52 (m, 6H), 1.04 – 0.95 (m, 15H), 0.93 (s, 9H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 203.3, 130.9, 126.5, 83.9, 69.8, 69.5, 61.0, 57.9, 41.2, 40.7, 38.8, 36.1, 26.2, 25.9, 18.5, 18.2, 18.2, 16.6, 13.0, 12.9, 9.6, -2.9, -4.1, -4.2, -4.5. HRMS calc *m/z* [$C_{29}H_{60}O_4Si_2$ + Na]$^{+}$: 551.3928, found: 551.3922.



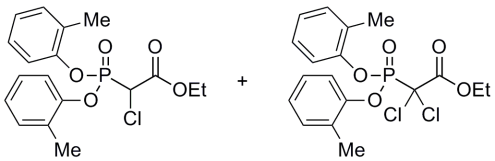
3.106a **3.108a**

Ethyl 2-(Bis(*o*-tolyloxy)phosphoryl)propanoate (3.106a) and Ethyl 2-(Bis(*o*-tolyloxy)phosphoryl)-2-methylpropanoate (3.108a). The product was synthesized following a previously reported procedure.[66] To a solution of phosphonate ester **3.107** (0.50 g, 1.4 mmol) in DMSO (5.3 mL) was added sodium hydride (60% in mineral oil, 0.057 g, 1.4 mmol). After stirring at room temperature for 20 min, iodomethane (0.10 mL, 1.6 mmol) was added to the reaction. After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The ^{31}P NMR spectra showed a 1.4:4.3:1 ratio of **3.107**:**3.106a**:**3.108a**. The crude material was purified via silica gel flash

chromatography (10% to 30% EtOAc in hexanes) to yield 0.284 g of product **3.106a** (55% yield) and 0.063 g of product **3.108a** (12% yield).

Ethyl 2-(bis(*o*-tolyloxy)phosphoryl)propanoate (**3.106a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.21 – 7.14 (m, 2H), 7.14 – 6.98 (m, 4H), 4.22 (qd, *J* = 7.1, 1.3 Hz, 2H), 3.43 (dq, *J* = 24.0, 7.3 Hz, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 1.69 (dd, *J* = 19.2, 7.3 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.8, 149.1, 149.0, 149.0, 131.4, 131.4, 129.3, 129.3, 129.2, 127.0, 127.0, 125.1, 125.1, 120.3, 120.2, 120.2, 120.2, 61.8, 40.08 (d, *J* = 136.5 Hz), 16.4, 14.0, 11.95 (d, *J* = 6.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.4. HRMS calc *m*/*z* $[C_{19}H_{23}O_5P + Na]^+$: 385.1175, found: 385.1211.

Ethyl 2-(Bis(*o*-tolyloxy)phosphoryl)-2-methylpropanoate (**3.108a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.19 – 7.11 (m, 2H), 7.12 – 6.96 (m, 4H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.24 (s, 6H), 1.72 (d, *J* = 17.7 Hz, 6H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 171.5, 149.6, 149.5, 131.2, 128.8, 128.8, 127.0, 126.9, 124.7, 120.0, 120.0, 61.9, 44.99 (d, *J* = 139.7 Hz), 21.40 (d, *J* = 4.6 Hz), 16.4, 13.9. ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.8. HRMS calc *m*/*z* $[C_{20}H_{25}O_5P + Na]^+$: 399.1332, found: 399.1335.



3.106b **3.108b**

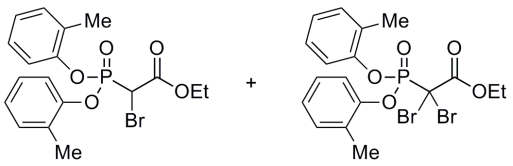
Ethyl 2-(Bis(*o*-tolyloxy)phosphoryl)-2-chloroacetate (3.106b) and Ethyl 2-(Bis(*o*-tolyloxy)phosphoryl)-2,2-dichloroacetate (3.108b). The synthesis was adapted from a previously reported procedure.[69] To a solution of phosphonate ester **3.107** (0.50 g, 1.4

mmol) in THF (7.2 mL) at 0 °C was added sodium hydride (60% in mineral oil, 0.069 g, 1.7 mmol) in two portions. After stirring at room temperature for 10 min, NCS (0.23 g, 1.7 mmol) was added to the reaction. After stirring for 10 min, the reaction was diluted with water. The mixture was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The ^{31}P NMR spectra showed a 1:2.3:2.1 ratio of **3.107**:**3.106b**:**3.108b**. The crude material was purified via silica gel flash chromatography (5% to 30% EtOAc in hexanes) to yield 0.163 g of product **3.106b** (30% yield) and 0.196 g of product **3.108b** (33% yield).

Ethyl 2-(bis(*o*-tolyloxy)phosphoryl)-2-chloroacetate (**3.106b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 2H), 7.22 – 7.17 (m, 2H), 7.17 – 7.04 (m, 4H), 4.86 (d, J = 16.1 Hz, 1H), 4.29 (qd, J = 7.2, 1.7 Hz, 2H), 2.27 (s, 6H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 148.9, 148.8, 148.8, 131.6, 131.5, 129.4, 129.4, 127.2, 127.1, 127.1, 127.1, 125.6, 125.6, 125.6, 120.2, 120.1, 120.1, 120.0, 63.5, 50.07 (d, J = 150.9 Hz), 16.3, 13.8. ^{31}P NMR (162 MHz, $CDCl_3$) δ 4.6. HRMS calc *m/z* $[C_{18}H_{20}ClO_5P + Na]^+$: 405.0629, found: 405.0617.

Ethyl 2-(bis(*o*-tolyloxy)phosphoryl)-2,2-dichloroacetate (**3.108b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 2H), 7.24 – 7.18 (m, 2H), 7.18 – 7.05 (m, 4H), 4.29 (q, J = 7.1 Hz, 2H), 2.31 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 162.7, 149.6, 149.5, 131.5, 129.1, 129.0, 127.1, 127.1, 125.5, 119.9, 119.9, 74.35 (d, J = 177.0 Hz), 65.0, 16.4, 13.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.2. HRMS calc *m/z*

$[C_{18}H_{19}Cl_2O_5P + Na]^+$: 439.0239, found: 439.0231.

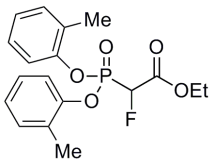


3.106c **3.108c**

Ethyl 2-(Bis(*o*-tolyloxy)phosphoryl)-2-bromoacetate (3.106c) and Ethyl 2-(Bis(*o*-tolyloxy)phosphoryl)-2,2-dibromoacetate (3.108c). The product was synthesized using the procedure for the synthesis of phosphonate ester **3.106b**. The reaction was performed with phosphonate ester **3.107** (1.2 g, 3.5 mmol) and 1,2-dibromotetrachloroethane (1.3 g, 4.1 mmol) instead of NCS. The ^{31}P NMR spectra showed a 1.7:10:1 ratio of **3.107**:**3.106c**:**3.108c**. The crude material was purified via silica gel flash chromatography (12% EtOAc in hexanes) to yield 0.811 g of product **3.106c** (55% yield). Ethyl 2-(bis(*o*-tolyloxy)phosphoryl)-2-bromoacetate (**3.106c**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H), 7.22 – 7.17 (m, 2H), 7.17 – 7.04 (m, 4H), 4.71 (d, *J* = 14.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 149.1, 149.0, 149.0, 148.9, 131.6, 131.5, 129.4, 129.4, 129.3, 129.3, 127.1, 127.1, 127.1, 127.0, 125.6, 125.5, 125.5, 120.1, 120.1, 120.1, 120.0, 63.5, 35.23 (d, *J* = 151.2 Hz), 16.4, 13.8. ^{31}P NMR (162 MHz, $CDCl_3$) δ 4.7. HRMS calc *m/z* $[C_{18}H_{20}BrO_5P + Na]^+$: 449.0124, found: 449.0229.

Ethyl 2-(bis(*o*-tolyloxy)phosphoryl)-2,2-dibromoacetate (**3.108c**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H), 7.23 – 7.17 (m, 2H), 7.17 – 7.05 (m, 4H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.34 (s, 6H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 163.1, 149.8, 149.7, 131.4, 129.1, 129.0, 127.0, 127.0, 125.4, 119.9, 119.9, 65.0, 45.87

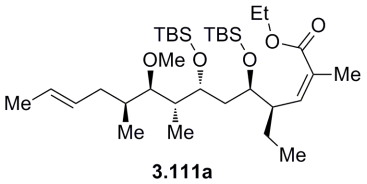
(d, J = 168.8 Hz), 16.6, 13.5. ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.3. HRMS calc m/z $[C_{18}H_{19}Br_2O_5P + Na]^+$: 526.9229, found: 526.9223.



3.106d

Ethyl 2-(Bis(o-tolyloxy)phosphoryl)-2-fluoroacetate (3.106d). To a solution of *o*-cresol (0.70 mL, 6.8 mmol) and triethylamine (1.0 mL, 7.2 mol) in toluene (5.2 mL) at 0 °C was cannula transferred a solution of ethyl dichlorophosphite (**3.109**, 0.40 mL, 3.5 mmol) in ether (2.1 mL). The reaction was warmed to room temperature and stirred overnight. The reaction was filtered through a fritted funnel and washed with toluene. The filtrate was filtered through a plug of basic alumina. Volatile materials were removed using a rotary evaporator. To the crude phosphite at 130 °C was added ethyl bromofluoroacetate (0.72 mL, 6.1 mmol) dropwise. After heating at 130 °C, overnight, the ^{31}P NMR spectra of the crude reaction showed no product. Additional bromofluoroacetate (0.36 mL, 3.0 mmol) was added to the reaction, and the reaction was heated to 180 °C overnight. The crude material was purified via silica gel flash chromatograph (20% EtOAc in hexanes) to yield 0.42 g of product as a colorless oil (41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 2H), 7.24 – 7.05 (m, 6H), 5.52 (dd, J = 46.7, 11.9 Hz, 1H), 4.31 (qq, J = 7.7, 3.5 Hz, 2H), 2.28 (s, 3H), 2.24 (s, 4H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (dd, J = 22.1, 1.3 Hz), 148.6, 148.5, 148.5, 148.4, 131.6, 131.6, 129.6, 129.5, 129.4, 127.2, 127.2, 127.1, 127.1, 125.8, 125.7, 120.3, 120.3, 120.2, 120.2, 84.1 (dd, J = 200.6, 162.8 Hz). 62.9, 16.2, 16.2,

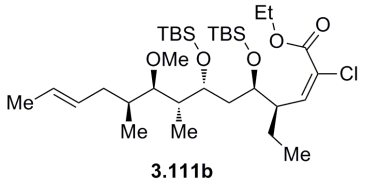
13.9. ^{31}P NMR (162 MHz, $CDCl_3$) δ 2.30 (d, J = 73.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -208.07 (d, J = 73.4 Hz). HRMS calc m/z $[C_{18}H_{20}FO_5P + Na]^+$: 389.0925, found: 389.0938.



3.111a

Ethyl (*2Z,4R,5R,7R,8R,9R,10S,12E*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)-4-ethyl-9-methoxy-2,8,10-trimethyltetradeca-2,12-dienoate (3.111a). To a solution of phosphonate ester **3.106a** (144 mg, 0.397 mmol) in THF (4.8 mL) at 0 °C was added sodium hydride (60% in mineral oil, 16 mg, 0.40 mmol). The reaction was stirred at 0 °C for 15 min before cooling to -78 °C. Aldehyde **3.103** (20.4 mg, 0.0386 mmol) was dissolved in THF (0.2 mL) and added to the reaction dropwise. The vial containing the aldehyde solution was rinsed with additional THF (0.2 mL) which was added to the reaction. The reaction was slowly warmed from -78 °C to ~0 °C over 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (6% ether in hexanes). The impure material was purified via silica gel flash chromatography (3%EtOAc in hexanes) to yield 20.7 mg of product as a colorless oil (87%). ^{1}H NMR (400 MHz, C_6D_6) δ 5.95 (dd, J = 10.0, 1.6 Hz, 1H), 5.62 – 5.35 (m, 2H), 4.37 (dd, J = 10.0, 4.6 Hz, 1H), 4.17 –

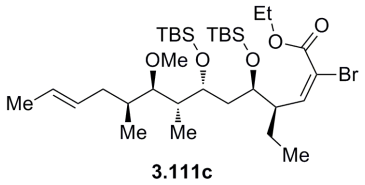
3.93 (m, 3H), 3.53 (s, 3H), 3.49 – 3.30 (m, 2H), 2.32 (dt, *J* = 15.0, 6.2 Hz, 1H), 2.15 (ddd, *J* = 13.6, 9.2, 4.7 Hz, 2H), 2.09 – 1.87 (m, 6H), 1.87 – 1.74 (m, 1H), 1.72 – 1.49 (m, 4H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.07 (t, *J* = 7.5 Hz, 3H), 1.04 – 1.00 (m, 21H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.26 (s, 3H), 0.23 (s, 3H), 0.17 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 167.4, 145.6, 131.3, 126.3, 84.1, 73.1, 69.4, 61.0, 60.0, 44.6, 42.1, 40.4, 39.0, 36.3, 26.3, 26.1, 21.7, 21.2, 18.6, 18.3, 18.2, 14.3, 13.2, 12.3, 9.7, -2.6, -4.0, -4.1, -4.4. HRMS calc *m*/*z* $[C_{34}H_{68}O_5Si_2 + Na]^+$: 635.4503, found: 635.4459.



3.111b

Ethyl (*2E,4R,5R,7R,8R,9R,10S,12E*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)-2-chloro-4-ethyl-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (3.111b). To a solution of phosphonate ester **3.106b** (66.2 mg, 0.173 mmol) in THF (5 mL) at 0 °C was added sodium hydride (60% in mineral oil, 5.8 mg, 0.14 mmol). After stirring at 0 °C for 15 min, a solution of aldehyde **3.103** (30.5 mg, 0.0577 mmol) in THF (0.2 mL) was added to the reaction dropwise. The vial containing the aldehyde solution was rinsed with additional THF (0.2 mL) and subsequently added to the reaction. The reaction was slowly warmed to room temperature over 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel

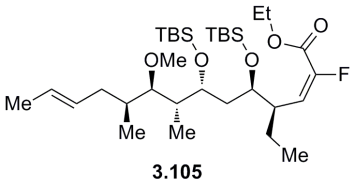
flash chromatography (6% ether in hexanes). The impure material was purified via silica gel flash chromatography (6%EtOAc in hexanes) to yield 6.8 mg of product **3.111b** as a colorless oil (19%) and 17.5 mg of unreacted aldehyde **3.103** (57%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.56 (d, *J* = 10.5 Hz, 1H), 5.60 – 5.39 (m, 2H), 4.30 (dd, *J* = 10.1, 4.6 Hz, 1H), 4.11 – 3.88 (m, 3H), 3.50 (s, 3H), 3.43 (ddd, *J* = 10.5, 7.4, 2.6 Hz, 1H), 3.35 (dd, *J* = 9.6, 1.7 Hz, 1H), 2.37 – 2.23 (m, 1H), 2.23 – 1.98 (m, 3H), 1.98 – 1.89 (m, 1H), 1.89 – 1.73 (m, 2H), 1.66 (dt, *J* = 3.3, 1.3 Hz, 3H), 1.62 – 1.48 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 9H), 1.00 – 0.92 (m, 18H), 0.22 (s, 3H), 0.20 (s, 3H), 0.13 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 162.6, 147.4, 131.2, 126.4, 122.9, 84.0, 72.5, 69.1, 61.8, 61.1, 45.6, 41.8, 40.4, 39.0, 36.2, 26.3, 26.1, 21.3, 18.6, 18.2, 18.2, 13.9, 13.2, 12.1, 9.6, -2.7, -4.1, -4.5. HRMS calc *m/z* $[C_{33}H_{65}ClO_5Si_2 + Na]^+$: 655.3951, found: 655.4024.



3.111c

Ethyl (*2E,4R,5R,7R,8R,9R,10S,12E*)-2-Bromo-5,7-bis((*tert*-butyldimethylsilyl)oxy)-4-ethyl-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (3.111c). To a suspension of sodium hydride (60% in mineral oil, 15 mg, 0.61 mmol) in THF (2 mL) at 0 °C was added a solution of phosphonate ester **3.106c** (283 mg, 0.662 mmol) in THF (1 mL). The vial containing the phosphonate ester was rinsed with additional THF (1 mL) and subsequently added to the reaction. After stirring at 0 °C for 20 min, a solution of aldehyde **3.103** (117 mg, 0.221 mmol) in THF (0.4 mL) was added to the reaction dropwise. The vial containing the aldehyde solution was rinsed with additional THF (0.4

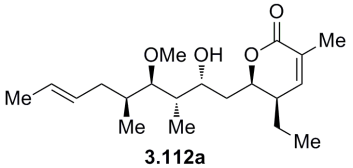
mL) which was added to the reaction. The reaction was slowly warmed to room temperature over 2 h. The reaction was quenched with saturated NH_4Cl. The layers were separated and the aqueous phase was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (5% ether in hexanes) to yield 38.9 mg of product **3.111c** as a colorless oil (25%) and 72.3 mg of unreacted aldehyde **3.103** (62%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.76 (d, *J* = 10.5 Hz, 1H), 5.60 – 5.35 (m, 2H), 4.27 (dd, *J* = 9.9, 4.7 Hz, 1H), 4.10 – 3.93 (m, 3H), 3.49 (s, 3H), 3.43 – 3.23 (m, 2H), 2.38 – 2.24 (m, 1H), 2.21 – 1.94 (m, 3H), 1.94 – 1.87 (m, 1H), 1.87 – 1.72 (m, 2H), 1.66 (dt, *J* = 4.6, 1.4 Hz, 3H), 1.63 – 1.48 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 9H), 1.00 – 0.92 (m, 18H), 0.21 (s, 3H), 0.19 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 162.9, 150.7, 131.2, 126.4, 111.6, 84.0, 72.4, 69.0, 61.9, 61.1, 47.0, 41.7, 40.4, 39.0, 36.2, 26.3, 26.1, 21.0, 18.6, 18.2, 18.2, 13.9, 13.2, 12.2, 9.6, -2.7, -4.1, -4.1, -4.5. HRMS calc *m/z* $[C_{33}H_{65}BrO_5Si_2 + Na]^+$: 699.3452, found: 699.3496.



3.105

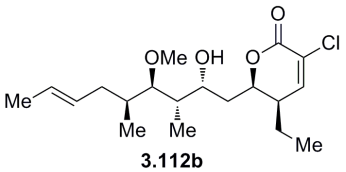
Ethyl (*2E,4R,5R,7R,8R,9R,10S,12E*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)-4-ethyl-2-fluoro-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (3.105). To a solution of phosphonate ester **3.106d** (105 mg, 0.287 mmol) in THF (2.5 mL) at 0 °C was added

sodium hydride (60% in mineral oil, 11 mg, 0.27 mmol). After stirring at 0 °C for 15 min, a solution of aldehyde **3.103** (15.2 mg, 0.0287 mmol) in THF (0.2 mL) was added to the reaction dropwise. The vial containing the aldehyde solution was rinsed with additional THF (0.2 mL) and subsequently added to the reaction. The reaction was slowly warmed to room temperature over 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4% ether in hexanes) to yield 11.1 mg of product as a colorless oil (63%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.03 (dd, *J* = 22.5, 10.8 Hz, 1H), 5.59 – 5.36 (m, 2H), 4.34 (dd, *J* = 9.8, 4.5 Hz, 1H), 4.08 – 3.89 (m, 3H), 3.62 – 3.47 (m, 4H), 3.35 (dd, *J* = 9.6, 1.7 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.22 – 2.12 (m, 1H), 2.11 – 2.03 (m, 1H), 2.03 – 1.84 (m, 3H), 1.84 – 1.74 (m, 1H), 1.73 – 1.58 (m, 3H), 1.48 (ddd, *J* = 13.7, 10.5, 7.2 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 9H), 0.99 – 0.89 (m, 18H), 0.23 (s, 3H), 0.21 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 161.0 (d, *J* = 35.2 Hz), 148.0 (d, *J* = 256.8 Hz), 131.2, 126.5, 126.2 (d, *J* = 16.6 Hz), 84.1, (d, *J* = 2.6 Hz), 69.4, 61.2, 61.1, 42.2 (d, *J* = 4.1 Hz), 41.9, 40.8, 39.0, 36.3, 26.3, 26.1, 21.9, 21.9, 18.7, 18.3, 18.3, 14.0, 13.2, 12.1, 9.8, -2.7, -4.0, -4.0, -4.4. ^{19}F NMR (376 MHz, C_6D_6) δ -119.4. HRMS calc *m/z* $[C_{33}H_{65}FO_5Si_2 + Na]^+$: 639.4539, found: 639.4198.



3.112a

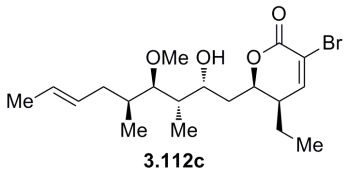
(*5R,6R*)-5-Ethyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-3-methyl-5,6-dihydro-2*H*-pyran-2-one (3.112a). A solution of ester **3.111a** (20.7 mg, 0.0338 mmol) in 1% HCl in ethanol (0.85 mL) was stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted four times with DCM. The combined organic layers were washed with brine and dried with Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (30% EtOAc in hexanes) to yield 8.5 mg of product **3.112a** as c colorless oil (74%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.04 (dd, *J* = 6.0, 1.6 Hz, 1H), 5.56 – 5.27 (m, 2H), 4.68 (dt, *J* = 8.1, 3.9 Hz, 1H), 4.51 – 4.34 (m, 1H), 3.15 (d, *J* = 2.6 Hz, 1H), 3.11 (s, 3H), 2.76 (dd, *J* = 6.3, 4.2 Hz, 1H), 2.15 – 1.97 (m, 1H), 1.90 – 1.75 (m, 5H), 1.76 – 1.53 (m, 7H), 1.43 – 1.26 (m, 2H), 1.21 (ddd, *J* = 13.3, 9.8, 7.1 Hz, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 3H), 0.66 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 165.1, 143.5, 129.5, 128.2, 126.9, 91.2, 77.6, 67.3, 61.4, 39.6, 39.6, 37.7, 37.6, 36.6, 21.1, 18.2, 17.4, 15.6, 11.9, 11.2. HRMS calc *m/z* $[C_{20}H_{34}O_4 + Na]^+$: 361.2349, found: 361.2331. >98% pure by UPLC analysis



3.112b

(*5R,6R*)-3-Chloro-5-ethyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (3.112b). The product was synthesized using the procedure for the synthesis of lactone **3.112a**. Reaction with ester **3.111b** (23.7 mg, 0.0374 mmol) resulted in 9.27 mg of product as a colorless oil (69%

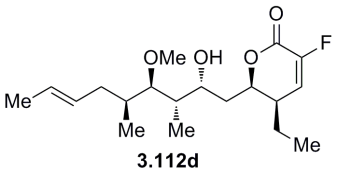
yield) stirring 48 h at room temperature and purification via silica gel flash chromatography (25% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.34 (d, *J* = 6.4 Hz, 1H), 5.59 – 5.28 (m, 2H), 4.62 – 4.46 (m, 1H), 4.27 (ddt, *J* = 8.9, 4.4, 2.0 Hz, 1H), 3.13 (d, *J* = 2.5 Hz, 1H), 3.09 (s, 3H), 2.73 (dd, *J* = 6.4, 4.1 Hz, 1H), 2.14 – 1.95 (m, 1H), 1.94 – 1.72 (m, 2H), 1.69 – 1.55 (m, 5H), 1.52 – 1.44 (m, 2H), 1.24 – 1.09 (m, 1H), 1.09 – 0.95 (m, 1H), 0.96 – 0.86 (m, 6H), 0.48 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 159.6, 145.1, 129.4, 127.1, 124.6, 91.2, 78.4, 67.2, 61.4, 41.0, 39.5, 37.5, 37.1, 36.6, 20.8, 18.2, 15.6, 11.9, 10.9. HRMS calc *m/z* $[C_{19}H_{31}ClO_4 + Na]^+$: 381.1803, found: 381.1799. >95% pure by UPLC analysis



3.112c

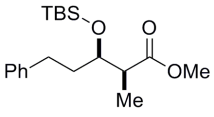
(*5R,6R*)-3-bromo-5-ethyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (3.112c). The product was synthesized using the procedure for the synthesis of lactone **3.112a**. Reaction with ester **3.111c** (10.5 mg, 0.0155 mmol) resulted in 5.36 mg of product as a white solid (86% yield) after stirring for 44 h at room temperature and purification via silica gel flash chromatography (25% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.72 (d, *J* = 6.4 Hz, 1H), 5.67 – 5.36 (m, 2H), 4.68 – 4.56 (m, 1H), 4.44 – 4.28 (m, 1H), 3.23 (s, 1H), 3.20 (s, 3H), 2.83 (dd, *J* = 6.4, 4.2 Hz, 1H), 2.24 – 2.05 (m, 1H), 1.98 – 1.80 (m, 2H), 1.80 – 1.63 (m, 5H), 1.63 – 1.50 (m, 2H), 1.32 – 1.20 (m, 1H), 1.20 – 1.09 (m, 1H), 1.03 (d, *J* = 6.3 Hz, 3H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.59 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 159.4, 150.1, 129.4, 127.0, 114.6, 91.1, 78.4, 67.2, 61.4, 42.2, 39.5, 37.5, 37.1, 36.6, 20.7, 18.2, 15.6,

11.9, 10.9. HRMS calc *m/z* $[C_{19}H_{31}BrO_4 + Na]^+$: 425.1298, found: 425.1323. >98% pure by UPLC analysis.



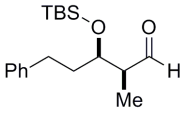
3.112d

(*5R,6R*)-5-ethyl-3-fluoro-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (3.112d). The product was synthesized using the procedure for the synthesis of lactone **3.112a**. Reaction with ester **3.105** (22.3 mg, 0.0361 mmol) resulted in 5.71 mg of product as a colorless oil (46% yield) after stirring for 42 h at room temperature and purification via silica gel flash chromatography (5% to 20% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 5.66 (dd, *J* = 11.1, 6.5 Hz, 1H), 5.53 – 5.29 (m, 2H), 4.57 (td, *J* = 6.8, 6.3, 3.7 Hz, 1H), 4.29 (t, *J* = 6.4 Hz, 1H), 3.18 (d, *J* = 2.4 Hz, 1H), 3.11 (s, 3H), 2.75 (dd, *J* = 6.4, 4.2 Hz, 1H), 2.12 – 1.95 (m, 1H), 1.87 – 1.72 (m, 2H), 1.68 – 1.57 (m, 5H), 1.54 – 1.45 (m, 2H), 1.25 – 1.12 (m, 1H), 1.10 – 0.96 (m, 1H), 0.93 (d, *J* = 4.9 Hz, 3H), 0.92 (d, *J* = 5.8 Hz, 3H), 0.50 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 158.70 (d, *J* = 31.1 Hz), 147.36 (d, *J* = 259.4 Hz), 129.5, 127.0, 122.55 (d, *J* = 10.2 Hz), 91.1, 78.6, 67.2, 61.4, 39.5, 38.70 (d, *J* = 3.7 Hz), 37.5, 37.2, 36.6, 21.05 (d, *J* = 3.2 Hz), 18.2, 15.6, 11.9, 10.8. ^{19}F NMR (376 MHz, C_6D_6) δ -127.1. HRMS calc *m/z* $[C_{19}H_{31}FO_4 + Na]^+$: 365.2099, found: 365.2078. >95% pure by UPLC analysis.



3.114

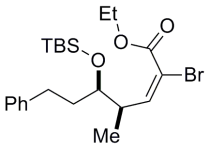
Methyl (*2,3-syn*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-5-phenylpentanoate (3.114). To a solution of alcohol **3.75** (0.52 g, 2.3 mmol) in DMF (1.6 mL) was added imidazole (0.24 g, 3.5 mmol) followed by TBSCl (0.53 g, 3.5 mmol). The reaction was stirred overnight, and then diluted with water. The mixture was extracted four times with ether. The combined organic layers were washed with brine and dried with $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (5% ether in hexanes) to yield 0.61 g of product as a colorless oil (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.11 (m, 3H), 4.07 (q, *J* = 5.5 Hz, 1H), 3.68 (s, 3H), 2.77 – 2.50 (m, 3H), 1.92 – 1.68 (m, 2H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 142.2, 128.4, 128.3, 125.8, 73.0, 51.5, 44.5, 37.2, 31.5, 25.8, 18.1, 11.4, -4.2, -4.7.



3.115

(*2,3-syn*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-5-phenylpentanal (3.115). To a solution of ester **3.114** (0.275 g, 0.817 mmol) in DCM (5.8 mL) at -78 °C, was added a solution of DIBAL-H (1 M in toluene, 1.6 mL, 1.6 mmol). After stirring at -78 °C for 15 min, the reaction was quenched with saturated aqueous Rochelle salt (8 mL). The mixture was warmed to room temperature and stirred for 1 h. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary

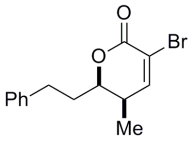
evaporator. The crude material was purified via silica gel flash chromatograph (5% ether in hexanes) to yield 0.13 g of product as a colorless oil (52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 1.0 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.24 – 7.10 (m, 3H), 4.16 (td, *J* = 6.4, 3.7 Hz, 1H), 2.80 – 2.63 (m, 1H), 2.63 – 2.49 (m, 2H), 1.83 (dtdd, *J* = 20.1, 13.6, 10.9, 6.1 Hz, 2H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 141.6, 128.5, 128.2, 126.0, 71.8, 51.3, 36.4, 32.2, 25.8, 25.7, 18.0, 7.9, -4.2, -4.6.



3.116

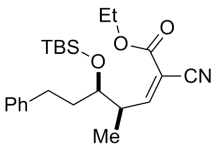
Ethyl (*4,5-syn,E*)-2-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-7-phenylhept-2-enoate (3.116). To a solution of phosphonate ester **3.106c** (0.92 g, 2.2 mmol) in THF (8 mL) at 0 °C was added sodium hydride (60% in mineral oil, 0.075 mg, 1.9 mmol). After stirring at 0 °C for 10 min, a solution of aldehyde **3.115** (0.33 g, 1.1 mmol) in THF (1 mL) was added to the reaction dropwise. The vial containing the aldehyde solution was rinsed with additional THF (1 mL) which was added to the reaction. The reaction was stirred at 0 °C for 2 h and quenched with saturated aqueous NH_4Cl. The mixture was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (2% ether in hexanes) to yield 0.37 g of product as a white solid (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.21 – 7.12 (m, 3H), 6.61 (d, *J* = 10.5 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.71 (td, *J* = 5.9, 4.5

Hz, 1H), 3.42 – 3.29 (m, 1H), 2.72 – 2.51 (m, 2H), 1.91 – 1.67 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 151.5, 142.2, 128.4, 128.3, 125.8, 110.4, 74.5, 62.1, 40.2, 36.9, 31.5, 25.9, 25.9, 18.1, 14.1, 13.9, -4.2, -4.6. mp: 61.4-63.4 °C.



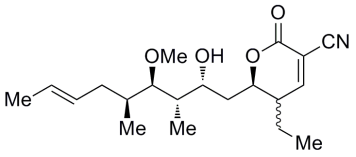
3.113

(*5,6-syn*)-3-Bromo-5-methyl-6-phenethyl-5,6-dihydro-2*H*-pyran-2-one (3.113). A solution of ester **3.116** (167 mg, 0.367 mmol) in 1% HCl in ethanol (3.5 mL) was stirred at room temperature for 48 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted four times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (20% ether in hexanes) to yield 83.5 mg of product as a white solid (77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.24 – 7.15 (m, 3H), 4.48 (dt, *J* = 9.4, 3.8 Hz, 1H), 2.90 (ddd, *J* = 14.3, 9.1, 5.3 Hz, 1H), 2.72 (ddd, *J* = 13.9, 8.9, 7.3 Hz, 1H), 2.45 (pd, *J* = 7.0, 3.4 Hz, 1H), 2.16 (dtd, *J* = 14.4, 9.2, 5.4 Hz, 1H), 1.80 (dddd, *J* = 13.7, 9.1, 7.3, 4.1 Hz, 1H), 1.10 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 151.2, 140.5, 128.6, 128.5, 126.3, 113.7, 79.6, 35.5, 33.0, 31.2, 11.2.



3.117

Ethyl (*4,5-syn,Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-cyano-4-methyl-7-phenylhept-2-enoate (3.117). Inside a glovebox under a nitrogen atmosphere, $[(^{t}Bu)_3PPdBr]_2$ (1.3 mg, 0.0017 mmol), zinc cyanide (7.1 mg, 0.060 mmol), acid washed Zn^0 (0.3 mg, 0.004 mmol) were added to a vial containing ester **3.116** (15.2 mg, 0.0334 mmol). After addition of DMF (0.33 mL) to the vial, the vial was sealed with a cap containing a PTFE/silicone septum and removed from the glovebox. The reaction was stirred overnight at room temperature. The reaction was diluted with water and the mixture was extracted four times with EtOAc. The combined organic layers were washed twice with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration through a plug of Celite® and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (5% EtOAc in hexanes) to yield 11.7 mg of product as a white solid (87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 10.8 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.23 – 7.14 (m, 4H), 4.32 (qd, *J* = 7.2, 2.9 Hz, 2H), 3.74 (td, *J* = 5.9, 4.3 Hz, 1H), 3.06 (dqd, *J* = 11.0, 6.8, 4.3 Hz, 1H), 2.66 (qdd, *J* = 13.7, 10.7, 5.7 Hz, 3H), 1.89 (ddt, *J* = 13.8, 11.1, 5.7 Hz, 1H), 1.75 (ddt, *J* = 13.7, 10.7, 6.1 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.07 (s, 3H), 0.05 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 161.3, 141.6, 128.5, 128.3, 126.0, 113.7, 108.8, 73.9, 62.5, 41.7, 36.5, 31.6, 25.8, 18.1, 14.1, 13.7, -4.2, -4.7.

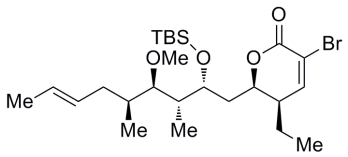


3.15

(*6R*)-5-Ethyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-

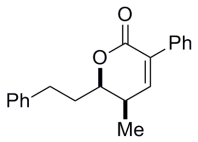
2-oxo-5,6-dihydro-2*H*-pyran-3-carbonitrile (3.15). Inside a glovebox under a nitrogen atmosphere, $[(^t\text{Bu})_3\text{PPdBr}]_2$ (1.7 mg, 0.0022 mmol), zinc cyanide (4.5 mg, 0.039 mmol), acid washed Zn^0 (1.2 mg, 0.018 mmol) were added to a vial containing ester **3.112c** (8.7 mg, 0.022 mmol). After addition of DMF (0.3 mL) to the vial, the vial was sealed with a cap containing a PTFE/silicone septum and removed from the glovebox. The reaction was stirred overnight at room temperature. The reaction was diluted with water and the mixture was extracted 5 times with EtOAc. The combined organic layers were washed twice with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration through a plug of Celite® and volatile materials were removed using a rotary evaporator. To the crude material was added 4 mg TMT^{129} and dissolved in 0.5 mL toluene. The suspension was stirred overnight and filtered through a plug of Celite®. Volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography to yield 5.1 mg of impure product as a colorless oil (66%) and 2.3 mg recovered starting material **3.112c**. HRMS calc *m*/*z* $[C_{20}H_{31}NO_4 + Na]^+$: 372.2151, found: 372.2089.

Mixture of Isomers: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.78 (d, *J* = 6.2 Hz, 0.5H), 7.58 (d, *J* = 3.7 Hz, 0.5H), 5.59 – 5.35 (m, 2H), 4.89 – 4.73 (m, 0.5H), 4.65 (ddd, *J* = 9.7, 7.1, 3.1 Hz, 0.5H), 4.29 – 4.08 (m, 1H), 3.55 – 3.39 (m, 3H), 3.31 (t, *J* = 9.7 Hz, 1H), 3.09 – 2.91 (m, 1H), 2.57 (tt, *J* = 7.8, 4.6 Hz, 1H), 2.11 (d, *J* = 11.8 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.93 – 1.40 (m, 10H), 1.17 – 0.75 (m, 9H).



3.119

(*5R,6R*)-3-Bromo-6-((*2R,3R,4R,5S,E*)-2-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5-ethyl-5,6-dihydro-2H-pyran-2-one (3.119). To a solution of alcohol **3.112c** (37.8 mg, 0.0937 mmol) and 2,6-lutidine (0.055 mL, 0.47 mmol) in DCM (3 mL) at -78 °C was added TBSOTf (0.043 mL, 0.19 mmol) dropwise. After stirring at -78 °C for 45 min, the reaction was quenched with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extract three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (10% EtOAc in hexanes) to yield 44.8 mg of product as a colorless oil (92% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 6.55 (d, *J* = 6.4 Hz, 1H), 5.50 – 5.35 (m, 2H), 4.38 – 4.22 (m, 2H), 3.38 (s, 3H), 3.19 (dd, *J* = 9.4, 1.9 Hz, 1H), 2.31 – 2.15 (m, 1H), 2.15 – 1.97 (m, 1H), 1.83 (ddd, *J* = 14.0, 9.2, 6.2 Hz, 1H), 1.70 (qd, *J* = 7.0, 1.7 Hz, 1H), 1.65 (d, *J* = 4.4 Hz, 3H), 1.62 – 1.43 (m, 3H), 1.12 (ddd, *J* = 13.5, 7.6, 4.7 Hz, 1H), 1.06 – 0.99 (m, 1H), 0.99 – 0.95 (m, 12H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.48 (t, *J* = 7.5 Hz, 3H), 0.13 (s, 6H). ^{13}C NMR (100 MHz, C_6D_6) δ 159.1, 149.9, 130.9, 126.6, 114.6, 84.2, 77.4, 68.7, 60.8, 42.0, 41.5, 38.8, 37.7, 36.2, 26.3, 20.7, 18.7, 18.3, 13.3, 10.9, 10.6, -3.5, -3.5. HRMS calc *m/z* $[C_{25}H_{45}BrO_4Si + Na]^+$: 539.2163, found: 539.2085.



3.121

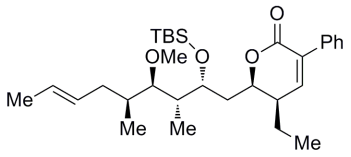
(*5,6-syn*)-5-Methyl-6-phenethyl-3-phenyl-5,6-dihydro-2*H*-pyran-2-one (3.121). Table 3-5, entry 3: Inside a glovebox under a nitrogen atmosphere, phenylboronic acid (5.9 mg, 0.048 mmol), potassium phosphate (11.3 mg, 0.0532 mmol) and $[(^t\text{Bu})_3\text{PPdBr}]_2$ (1.3 mg, 0.0016 mmol) were added to a vial containing lactone **3.113** (9.54 mg, 0.0323 mmol). The mixture was suspended in THF (0.3 mL) and acetonitrile (0.2 mL). The vial was sealed with a cap containing a PTFE/silicone septum and removed from the glovebox. Degassed water (0.1 mL) was added to the reaction and the suspension was stirred at room temperature for 3 h. The reaction was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dry with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. 1,3,5-Trimethoxybenzene (1.54 mg) was added to the crude material for calculating the yield via ^{1}H NMR spectroscopy (74% NMR yield). The crude material was purified via silica gel flash chromatography (12% EtOAc in hexanes) to yield 8.98 mg of product as a colorless oil (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 2H), 7.41 – 7.27 (m, 5H), 7.27 – 7.17 (m, 3H), 6.99 (d, *J* = 6.4 Hz, 1H), 4.51 (dt, *J* = 9.4, 3.9 Hz, 1H), 2.95 (ddd, *J* = 14.5, 9.6, 5.4 Hz, 1H), 2.76 (ddd, *J* = 13.9, 9.2, 7.0 Hz, 1H), 2.53 (pd, *J* = 7.0, 3.4 Hz, 1H), 2.30 – 2.12 (m, 1H), 1.84 (dddd, *J* = 13.9, 9.6, 7.0, 4.3 Hz, 1H), 1.13 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 147.2, 141.0, 135.3, 131.8, 129.6, 128.6, 128.5, 128.3, 128.2, 128.2, 126.2, 78.9,

33.2, 32.9, 31.4, 11.4.

Table 3-5, entry 2: Inside a glovebox under a nitrogen atmosphere, phenylboronic acid (5.8 mg, 0.048 mmol), potassium fluoride (8.3 mg, 0.14 mmol) and $[(^t\text{Bu})_3\text{PPdBr}]_2$ (1.2 mg, 0.0016 mmol) were added to a vial containing lactone **3.113** (9.36 mg, 0.0317 mmol). The mixture was suspended in THF (0.4 mL). The vial was sealed with a cap containing a PTFE/silicone septum and removed from the glovebox. Degassed water (1.1 μL, 0.063 mmol) was added to the reaction and the suspension was stirred at room temperature for 5.5 h. The reaction was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dry with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. 1,3,5-Trimethoxybenzene (1.47 mg) was added to the crude material for calculating the yield via ^{1}H NMR spectroscopy (94% NMR yield)

Table 3-5, entry 4: Inside a glovebox under a nitrogen atmosphere, phenylboronic acid (5.9 mg, 0.048 mmol), potassium phosphate (13.8 mg, 0.0650 mmol) and Xphos Pd G2 (2.63 mg, 0.00334 mmol) were added to a vial containing lactone **3.113** (9.58 mg, 0.0325 mmol). The mixture was suspended in THF (0.2 mL). The vial was sealed with a cap containing a PTFE/silicone septum and removed from the glovebox. Degassed water (0.4 mL) was added to the reaction and the reaction was stirred at room temperature for 3 h. The reaction was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dry with anhydrous Na_2SO_4. The salts were removed via gravity

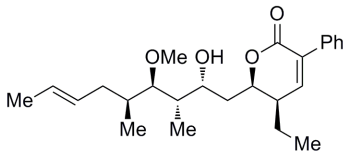
filtration and volatile materials were removed using a rotary evaporator. 1,3,5-Trimethoxybenzene (1.39 mg) was added to the crude material for calculating the yield via ^{1}H NMR spectroscopy (76% NMR yield).



3.123

(*5R,6R*)-6-((*2R,3R,4R,5S,E*)-2-((*tert*-Butyldimethylsilyl)oxy)-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5-ethyl-3-phenyl-5,6-dihydro-2*H*-pyran-2-one (3.123). Inside a glovebox under a nitrogen atmosphere, phenyl boronic acid (7.4 mg, 0.060 mmol), potassium phosphate (14.1 mg, 0.0664 mmol) and $[(^t\text{Bu})_3\text{PPdBr}]_2$ (1.6 mg, 0.0020 mmol) were added to a vial containing lactone **3.119** (20.8 mg, 0.0402 mmol). The mixture was suspended in THF (0.3 mL) and acetonitrile (0.2 mL). The vial was sealed with cap containing a PTFE/silicone septum and removed from the glovebox. Degassed water (0.1 mL) was added to reaction and the suspension was stirred at room temperature for 6 h. The reaction was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted four times with EtOAc. The combined organic layers were washed with brine and dry with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (17% ether in hexanes). Impure material was further purified via silica gel flash chromatography (15% ether in hexanes). To the combined product was added 8 mg TMT[129] and suspended in toluene (1 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to yield 11.18 mg product as a colorless oil

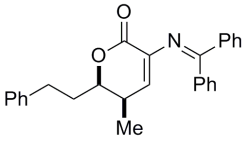
(54% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.62 – 7.54 (m, 2H), 7.24 – 7.09 (m, 3H), 6.52 (d, *J* = 6.3 Hz, 1H), 5.55 – 5.35 (m, 2H), 4.54 (dt, *J* = 8.8, 4.1 Hz, 1H), 4.46 (ddd, *J* = 7.7, 5.9, 1.6 Hz, 1H), 3.43 (s, 3H), 3.26 (dd, *J* = 9.3, 1.9 Hz, 1H), 2.32 – 2.19 (m, 1H), 2.15 – 2.04 (m, 1H), 1.99 (ddd, *J* = 14.8, 9.3, 5.8 Hz, 1H), 1.85 (dq, *J* = 9.8, 4.8 Hz, 1H), 1.79 – 1.61 (m, 6H), 1.41 – 1.20 (m, 2H), 1.10 – 0.93 (m, 12H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.68 (t, *J* = 7.5 Hz, 3H), 0.23 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 163.3, 145.4, 136.5, 133.2, 131.0, 128.9, 126.6, 84.3, 76.5, 69.0, 60.8, 42.2, 39.3, 38.8, 38.0, 36.2, 26.3, 21.1, 18.7, 18.2, 13.3, 11.2, 10.7, -3.5. HRMS calc *m/z* $[C_{31}H_{50}O_4Si + Na]^+$: 537.3371, found: 537.3301.



3.122

(*5R,6R*)-5-Ethyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-3-phenyl-5,6-dihydro-2*H*-pyran-2-one (3.122). To a solution of lactone **3.123** (10.21 mg, 0.01983 mmol) in $CHCl_3$ (0.8 mL) at 0 °C was added dropwise BF_3•Et_2O (0.020 mL, 0.16 mmol). The reaction was stirred at 0 °C for 40 min and then quenched with saturated aqueous $NaHCO_3$ and diluted with DCM. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dry with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (20% EtOAc in hexanes) to yield 6.93 mg of product as a colorless oil (87% yield). ^{1}H NMR (400 MHz, C_6D_6) δ

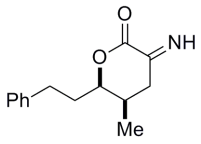
7.60 – 7.53 (m, 2H), 7.22 – 7.10 (m, 3H), 6.56 (d, *J* = 6.2 Hz, 1H), 5.56 – 5.27 (m, 2H), 4.78 (dt, *J* = 8.1, 3.9 Hz, 1H), 4.51 – 4.40 (m, 1H), 3.19 (d, *J* = 2.1 Hz, 1H), 3.12 (s, 3H), 2.78 (dd, *J* = 6.3, 4.3 Hz, 1H), 2.15 – 1.99 (m, 1H), 1.93 – 1.77 (m, 3H), 1.77 – 1.58 (m, 6H), 1.47 – 1.18 (m, 2H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H), 0.69 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 163.6, 145.7, 136.6, 133.0, 129.5, 129.0, 127.0, 91.2, 77.5, 67.4, 61.4, 39.9, 39.7, 37.6, 37.5, 36.6, 21.1, 18.2, 15.6, 12.0, 11.3. HRMS calc *m/z* $[C_{25}H_{36}O_4 + Na]^+$: 423.2506, found: 423.2459. >96% pure by UPLC analysis.



3.126

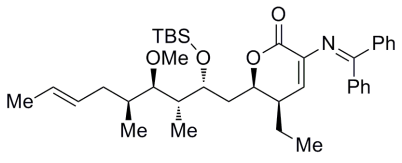
(*5,6-syn*)-3-((Diphenylmethylene)amino)-5-methyl-6-phenethyl-5,6-dihydro-2*H*-pyran-2-one (3.126). Inside a glovebox under a nitrogen atmosphere, benzophenone imine (6.7 mg, 0.037 mmol), potassium phosphate (16.4 mg, 0.0773 mmol), 1,3,5-trimethoxybenzene (3.4 mg, 0.030 mmol), $Pd_2(dba)_3$ (5.7 mg, 0.0062 mmol), and ^{t}Bu-Xphos (7.9 mg, 0.018 mmol) were added to a vial containing lactone **3.113** (6.7 mg, 0.031 mmol). The mixture was suspended in DME (0.3 mL). The vial was sealed with a cap containing a PTFE/silicone septum and removed from the glovebox and stirred at 30 °C for 18 h. The reaction was diluted with water and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. ^{1}H NMR analysis of the crude material showed the product was synthesized in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.67 (m, 2H), 7.49 – 7.43 (m, 1H), 7.42 – 7.27 (m, 7H), 7.26 – 7.09 (m, 5H), 5.86 (d, *J* = 6.5 Hz, 1H), 4.19 (dt, *J* = 9.5, 3.8 Hz, 1H),

2.81 (ddd, *J* = 14.1, 9.0, 5.3 Hz, 1H), 2.63 (dt, *J* = 14.0, 8.1 Hz, 1H), 2.24 (td, *J* = 6.9, 3.3 Hz, 1H), 2.11 – 1.94 (m, 1H), 1.66 (dddd, *J* = 13.4, 9.2, 7.7, 4.1 Hz, 1H), 0.80 (d, *J* = 7.0 Hz, 3H).



3.127

(*5,6-syn*)-3-Imino-5-methyl-6-phenethyltetrahydro-2*H*-pyran-2-one (3.127). Imine **3.126** (9.4 mg, 0.024 mmol) and hydroxylamine hydrochloride (6.6 mg, 0.095 mmol) were dissolved in THF (0.4 mL) and water (0.4 mL) and stirred at room temperature for 16 h. The mixture was then extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (40% EtOAc in hexanes) to yield 3.12 mg of product as a colorless oil (57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.13 (m, 3H), 4.34 (dt, *J* = 10.1, 3.1 Hz, 1H), 2.92 (ddd, *J* = 14.3, 9.3, 5.1 Hz, 1H), 2.85 – 2.58 (m, 3H), 2.31 – 2.17 (m, 1H), 2.06 (dtd, *J* = 14.0, 9.4, 5.1 Hz, 1H), 1.83 (dddd, *J* = 13.6, 9.9, 7.9, 3.7 Hz, 1H), 1.02 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 146.8, 140.7, 128.6, 128.5, 126.3, 81.3, 33.4, 31.5, 29.9, 29.1, 13.4. HRMS calc *m/z* $[C_{14}H_{17}NO_2 + K]^+$: 270.0891, found: 270.1168.

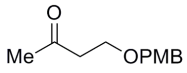


3.128

(*5R,6R*)-6-((*2R,3R,4R,5S,E*)-2-((*tert*-Butyldimethylsilyl)oxy)-4-methoxy-3,5-dimethylnon-7-en-1-yl)-3-((diphenylmethylene)amino)-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (3.128). Inside a glovebox under a nitrogen atmosphere, benzophenone imine (6.4 mg, 0.035 mmol), potassium phosphate (15.6 mg, 0.0735 mmol), $Pd_2(dba)_3$ (13.5 mg, 0.0147 mmol), and ^{t}Bu-Xphos (15.0 mg, 0.0353 mmol) were added to a vial containing lactone **3.119** (15.2 mg, 0.0294 mmol). The mixture was suspended in DME (0.4 mL). The vial was sealed with a cap containing a PTFE/silicone septum and removed from the glovebox and stirred at 30 °C for 10 h. The reaction was diluted with water and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The crude material was initially purified via silica gel column chromatography (5% to 40% ether in hexanes). The impure material was further purified via silica gel column chromatography (10% EtOAc in hexanes) to yield 1.65 mg of product as a colorless oil (9% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.99 – 7.90 (m, 2H), 7.23 – 7.13 (m, 2H), 7.14 – 7.00 (m, 6H), 5.50 (d, *J* = 6.5 Hz, 1H), 5.48 – 5.37 (m, 2H), 4.42 (dt, *J* = 8.6, 4.3 Hz, 1H), 4.34 (t, *J* = 6.7 Hz, 1H), 3.40 (s, 3H), 3.23 (dd, *J* = 9.3, 1.8 Hz, 1H), 2.31 – 2.18 (m, 1H), 2.16 – 2.04 (m, 1H), 1.88 (ddd, *J* = 14.7, 8.9, 6.2 Hz, 1H), 1.74 (qt, *J* = 7.9, 4.6 Hz, 2H), 1.69 – 1.56 (m, 5H), 1.33 – 1.20 (m, 1H), 1.11 – 0.94 (m, 13H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.40 (t, *J* = 7.4 Hz, 3H), 0.15 (s, 6H). ^{13}C NMR (100 MHz, C_6D_6) δ 171.3, 161.3, 140.8, 139.0, 136.8, 131.2, 131.0, 129.9, 128.7, 128.6, 128.4, 127.2, 126.5, 84.1, 77.2, 68.9, 60.8, 41.9, 38.8, 38.3, 38.2, 36.2, 26.3, 21.4, 18.7, 18.2, 13.3, 10.8, 10.4, -3.4, -3.5. HRMS calc *m/z* $[C_{38}H_{55}NO_4Si + Na]^+$: 640.3793, found: 640.3756.

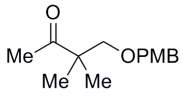
6.4 Chapter 4 experimental procedures.

6.4.1 Synthetic procedures and compound characterization data



4.11a

4-((4-Methoxybenzyl)oxy)butan-2-one (4.11a). 4-Hydroxy-2-butanone (0.20 mL, 2.3 mmol), diisopropylethylamine (0.80 mL, 4.6 mmol) and 4-methoxybenzyl chloride (0.35 mL, 2.6 mmol) were stirred in a sealed vial at 150 °C. After 2.5 h, the reaction was cooled to room temperature and dilutes with EtOAc and 10% aqueous sodium bisulfate. The layers were separated and the aqueous phase was extract three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The suspension was filtered and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (5:1 hexanes:EtOAc) to yield 0.16 g of product as a colorless oil (34% yield). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[130]

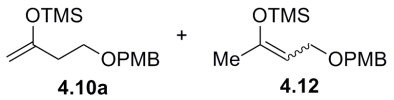


4.11b

4-((4-Methoxybenzyl)oxy)-3,3-dimethylbutan-2-one (4.11b). 4-Hydroxy-3,3-dimethylbutan-2-one was synthesized following previously reported procedure. A solution of 3-methyl-2-butanone (2.0 mL, 19 mmol) and paraformaldehyde (0.56 g) in trifluoroacetic acid (2.8 mL) was heated overnight at 90 °C in a round bottom flask equipped with a reflux condenser. The reaction was cooled to room temperature and

quenched with saturated aqueous $NaHCO_3$. The mixture was extracted three times with DCM and the combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The suspension was filtered and volatile materials were removed using a rotary evaporator. The impure material was purified via silica gel flash chromatography (35% EtOAc in hexanes) to yield 0.40 g of product as a colorless oil (18% yield). The resonances in the ^1H NMR spectrum of the intermediate ketone matched previously reported chemical shifts.[131]

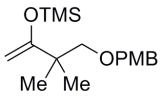
Ketone **4.11b** was synthesized following the procedure for the synthesis of ketone **4.11a**. Reaction with 4-hydroxy-3,3-dimethylbutan-2-one (0.40 g, 3.4 mmol) yielded 0.54 g of product as a colorless oil (67% yield) following purification via Combiflash® silica gel flash chromatography (1% to 10% EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 6.91 – 6.83 (m, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.41 (s, 2H), 2.13 (s, 3H), 1.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 159.1, 130.3, 129.1, 113.7, 77.2, 73.0, 55.3, 48.6, 25.8, 22.0. HRMS calc *m/z* $[C_{14}H_{20}O_3 + Na]^+$: 259.1305, found: 259.1284.



4.10a **4.12**

((4-((4-Methoxybenzyl)oxy)but-1-en-2-yl)oxy)trimethylsilane (4.10a) and ((4-((4-Methoxybenzyl)oxy)but-2-en-2-yl)oxy)trimethylsilane (4.12). To diisopropylamine (0.16 mL, 1.1 mmol) in THF (1.4 mL) at 0 °C was added a solution of *n*-butyllithium (2.5 M in hexanes, 0.48 mL, 1.2 mmol) dropwise. After 25 min, the reaction was cooled to -78 °C. A solution of ketone **4.11a** (0.16 g, 0.75 mmol) in THF (0.6 mL) was added dropwise. After 15 min, chlorotrimethylsilane (0.14 mL, 1.1 mmol) was added and the

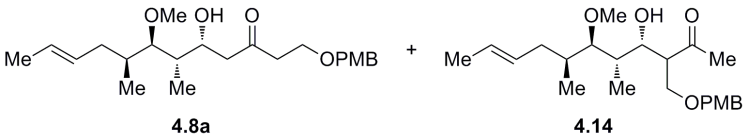
reaction was warmed to room temperature over 2 h. The reaction was diluted with pentane and washed with saturated aqueous $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed by rotary evaporator. ^1H NMR analysis of the crude material showed a 1.1:1 mixture of **4.10a** and **4.12**. The crude mixture was used without further purification.



4.10b

((4-((4-Methoxybenzyl)oxy)-3,3-dimethylbut-1-en-2-yl)oxy)trimethylsilane (4.10b). The procedure was adapted from a previously report procedure.[50] To THF (11.4 mL) was added a solution of lithium bis(trimethylsilyl)amide (1 M in hexanes, 1.9 mL, 1.9 mmol) and the solution was cooled to -78 °C. Ketone **4.11b** (0.18 g, 0.75 mmol) was dissolved in a separate vial in THF (0.6 mL) and added to the reaction dropwise. The vial containing the solution of with ketone **4.11b** was rinsed with additional THF (0.3 mL) which was added to the reaction. The reaction was stirred at -78 °C for 40 min. Then a mixture of TEA/TMSCl (1:1 v/v, filter through Celite(R), 0.24 mL) was added to the reaction and stirred at -78 °C for 20 min. The reaction was warmed to room temperature and concentrated to ~ 1 mL. The reaction was diluted with a 4:1 hexanes:diethyl ether solution (12 mL) and concentrated using a rotary evaporator. The crude material was resuspended in a 4:1 hexanes:diethyl ether solution (12 mL) and concentrated using a rotary evaporator and repeated once. The crude material was resuspended in a 4:1 hexanes:diethyl ether (12 mL) solution and filter through Celite®. Volatile materials

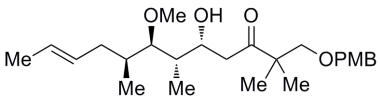
were removed by rotary evaporator. The crude silyl enol ether was used without further purification.



(*5R,6S,7R,8S,E*)-5-Hydroxy-7-methoxy-1-((4-methoxybenzyl)oxy)-6,8-dimethyldodec-10-en-3-one (4.8a) and (*4S,5S,6R,7S,E*)-4-Hydroxy-6-methoxy-3-(((4-methoxybenzyl)oxy)methyl)-5,7-dimethylundec-9-en-2-one (4.14). A suspension of alcohol **4.13** (35 mg, 0.19 mmol), NMO (26 mg, 0.23 mmol), and powdered 4Å molecular sieves (50 mg) was stirred in DCM (1 mL) at 0 °C for 15 min. A solution of TPAP (6.6 mg, 0.019 mmol) in DCM (0.3 mL) was added to the reaction. After stirring at 35 min at 0 °C, the reaction was diluted with 40% EtOAc in hexanes and filtered through a plug of silica gel. The silica gel plug was rinsed with 40% acetate in hexanes. The crude aldehyde solution was concentrated using a rotary evaporator the crude aldehyde was used without further purification.

The crude aldehyde was combined with crude silyl enol ethers **4.10a/4.12** (~0.75 mmol) and dissolved in DCM (1.7 mL) and cooled in a MeOH/*lq* N_2 bath. $BF_3 \bullet Et_2O$ (0.47 mL, 0.94 mmol) was added dropwise and the reaction was stirred in the MeOH/*lq* N_2 bath for 2.25 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and warmed to room temperature. The layers were separated and the aqueous phase was extracted three times with DCM and once with EtOAc. The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed by rotary evaporator. The crude

material was initially purified via Combiflash® silica gel flash chromatography (5% to 30% EtOAc in hexanes) and subsequently purified silica gel column (25% EtOAc in hexanes and 30% EtOAc in hexanes) to yield 24.7 mg of **4.8a** (35% yield) and 9.0 mg of **4.14** (12% yield). **4.8a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 1H), 6.96 – 6.82 (m, 2H), 5.53 – 5.30 (m, 2H), 4.43 (s, 3H), 3.80 (s, 3H), 3.71 (t, *J* = 6.3 Hz, 2H), 3.48 (s, 3H), 3.34 (d, *J* = 2.6 Hz, 1H), 3.08 (dd, *J* = 7.1, 4.5 Hz, 1H), 2.80 – 2.64 (m, 3H), 2.46 (dd, *J* = 16.7, 3.5 Hz, 1H), 2.22 – 2.09 (m, 1H), 2.01 – 1.88 (m, 1H), 1.75 (ddd, *J* = 12.8, 7.8, 5.6 Hz, 1H), 1.70 – 1.63 (m, 3H), 1.63 – 1.55 (m, 1H), 0.88 (d, *J* = 2.6 Hz, 3H), 0.86 (d, *J* = 2.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 159.2, 130.0, 129.6, 129.4, 126.6, 113.8, 87.8, 72.9, 66.8, 64.9, 61.6, 55.3, 48.2, 43.6, 39.4, 37.5, 35.9, 18.0, 13.7, 10.9. HRMS calc *m/z* $[C_{23}H_{36}O_5 + Na]^+$: 415.2455, found: 415.2490 . **4.14**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 2H), 6.91 – 6.81 (m, 2H), 5.51 – 5.26 (m, 2H), 4.50 – 4.34 (ABq, 2H), 4.18 (dd, *J* = 9.9, 1.5 Hz, 1H), 3.86 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.80 (s, 3H), 3.71 (t, *J* = 8.9 Hz, 1H), 3.55 (s, 1H), 3.46 (s, 3H), 3.08 (ddd, *J* = 9.9, 8.8, 4.8 Hz, 1H), 2.91 (dd, *J* = 7.1, 3.6 Hz, 1H), 2.17 (s, 3H), 2.12 – 1.99 (m, 1H), 1.86 – 1.74 (m, 2H), 1.71 – 1.54 (m, 4H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 159.1, 130.1, 129.2, 128.5, 126.9, 113.7, 91.0, 73.0, 70.2, 69.4, 61.9, 56.6, 55.2, 36.5, 36.3, 36.0, 31.4, 18.0, 15.3, 11.6. . HRMS calc *m/z* $[C_{23}H_{36}O_5 + Na]^+$: 415.2455, found: 415.2538.

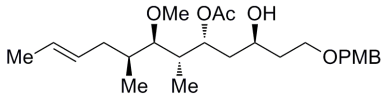


4.8b

(*5R,6S,7R,8S,E*)-5-Hydroxy-7-methoxy-1-((4-methoxybenzyl)oxy)-2,2,6,8-tetramethyldodec-10-en-3-one (4.8b). A suspension of alcohol **4.13** (40. mg, 0.22 mmol), NMO (30. mg, 0.25 mmol), and powdered 4Å molecular sieves (50 mg) was stirred in DCM (1.5 mL) at 0 °C for 20 min. A solution of TPAP (6.5 mg, 0.021 mmol) in DCM (0.5 mL) was added to the reaction. After stirring at 1 h at 0 °C, the reaction was diluted with 40% EtOAc in hexanes and filtered through a plug of silica gel. The silica gel plug was rinsed with 40% acetate in hexanes. The crude aldehyde solution was concentrated using a rotary evaporator the crude aldehyde was used without further purification.

The crude aldehyde was combined with crude silyl enol ethers **4.10b** (~0.75 mmol) and dissolved in DCM (2 mL) and cooled in a MeOH/*lq* N_2 bath. BF_3•Et_2O (0.20 mL, 1.6 mmol) was added dropwise and the reaction was stirred in the MeOH/*lq* N_2 bath for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and warmed to room temperature. The layers were separated and the aqueous phase was extracted three times with DCM and once with EtOAc. The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed by rotary evaporator. The crude material was initially purified via Combiflash® silica gel flash chromatography (5% to 10% EtOAc in hexanes) and subsequently purified via silica gel column (2% diethyl ether in DCM) to yield 46.6 mg of product as a colorless oil (52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 2H), 6.98 – 6.81 (m, 2H), 5.58 – 5.35 (m, 2H), 4.48 – 4.36 (m, 3H), 3.80 (s, 3H), 3.50 (s, 3H), 3.40 (s, 2H), 3.38 (d, *J* = 2.0 Hz, 1H), 3.12 (dd, *J* = 7.7,

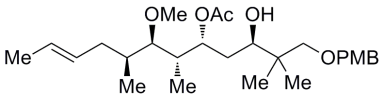
4.0 Hz, 1H), 2.67 (dd, *J* = 17.8, 8.7 Hz, 1H), 2.56 (dd, *J* = 17.7, 3.7 Hz, 1H), 2.17 (dt, *J* = 12.2, 5.4 Hz, 1H), 1.97 (dt, *J* = 13.2, 7.1 Hz, 1H), 1.84 – 1.70 (m, 1H), 1.66 (d, *J* = 5.1 Hz, 3H), 1.57 – 1.51 (m, 1H), 1.13 (s, 3H), 1.12 (s, 3H), 0.86 (d, *J* = 7.4 Hz, 3H), 0.84 (d, *J* = 7.4 Hz, 3H). HRMS calc *m/z* $[C_{25}H_{40}O_5 + Na]^+$: 443.2768, found: 443.2775.



4.15a

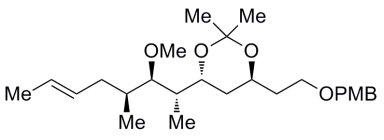
(*3S,5R,6S,7R,8S,E*)-3-Hydroxy-7-methoxy-1-((4-methoxybenzyl)oxy)-6,8-dimethyldodec-10-en-5-yl Acetate (4.15a). To a solution of ketone **4.8a** (68 mg, 0.17 mmol) in THF (0.7 mL) in a MeOH/ice bath was added acetaldehyde (0.078 mL, 1.4 mmol) followed by a solution of SmI_2 (0.06 M in THF, 1.2 mL, 0.069 mmol). The reaction was stirred in a MeOH/ice bath for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and warmed to room temperature. The layers were separated and the aqueous phased was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (25% EtOAc in hexanes) to yield 61.1 mg of product as a colorless oil (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 10.7 Hz, 3H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.56 – 5.32 (m, 3H), 4.43 (s, 2H), 3.80 (s, 3H), 3.73 – 3.52 (m, 3H), 3.37 (s, 3H), 2.82 (dd, *J* = 9.4, 2.2 Hz, 1H), 2.21 – 2.06 (m, 4H), 2.08 – 1.90 (m, 1H), 1.84 – 1.70 (m, 3H), 1.70 – 1.55 (m, 5H), 1.46 (ddd, *J* = 13.8, 10.3, 3.2 Hz, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 159.1, 130.4, 130.1, 129.2, 126.4, 113.7,

85.3, 72.7, 71.1, 67.4, 65.4, 61.3, 55.2, 41.4, 40.2, 38.3, 36.7, 35.7, 21.1, 17.9, 12.3, 10.5. HRMS calc *m/z* $[C_{25}H_{40}O_6 + Na]^+$: 459.2717, found: 459.2736.



4.15b

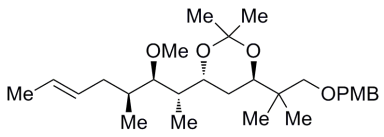
(*3R,5R,6S,7R,8S,E*)-3-Hydroxy-7-methoxy-1-((4-methoxybenzyl)oxy)-2,2,6,8-tetramethyldodec-10-en-5-yl Acetate (4.15b). The product was synthesized following the procedure for the synthesis of intermediate **4.15a**. Reaction with ketone **4.8b** (46.9, 0.112 mmol) yielded 49.8 mg of product as a colorless oil (96% yield) following purification via silica gel flash chromatography (15% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 2H), 6.96 – 6.80 (m, 2H), 5.56 – 5.28 (m, 3H), 4.42 (s, 2H), 3.80 (s, 3H), 3.44 – 3.34 (m, 2H), 3.39 (s, 3H), 3.34 – 3.19 (ABq, 2H), 2.84 (dd, *J* = 9.4, 2.1 Hz, 1H), 2.19 – 2.09 (m, 1H), 2.08 (s, 3H), 2.05 – 1.91 (m, 1H), 1.82 – 1.70 (m, 2H), 1.71 – 1.63 (m, 4H), 1.42 (ddd, *J* = 14.1, 10.6, 3.5 Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). HRMS calc *m/z* $[C_{27}H_{44}O_6 + Na]^+$: 487.3030, found: 487.3016.



4.16a

(*4R,6S*)-4-((*2S,3R,4S,E*)-3-Methoxy-4-methyloct-6-en-2-yl)-6-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxane (4.16a). To a solution of ester **4.15a** (7.0 mg, 0.016 mmol) in methanol (0.6 mL) was added potassium hydroxide (4.5 mg, 0.080 mmol). After stirring at room temperature for 3.5 h, the reaction was poured

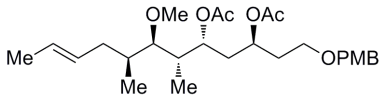
into saturated aqueous NH_4Cl. The mixture was extracted four times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was dissolved in 2,2-dimethoxypropane (1 mL) and PPTS (1 mg, 0.004 mmol) was added to the reaction. After stirring overnight at room temperature, the reaction was diluted with DCM and saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. Crude material was purified via silica gel flash chromatography (10% EtOAc in hexanes) to yield 4.0 mg of product as a colorless oil (58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 2H), 6.96 – 6.82 (m, 2H), 5.56 – 5.33 (m, 2H), 4.43 (s, 2H), 4.13 (ddd, *J* = 9.2, 6.9, 2.4 Hz, 1H), 3.93 (dd, *J* = 11.3, 5.4 Hz, 1H), 3.80 (s, 3H), 3.59 – 3.50 (m, 2H), 3.46 (s, 3H), 3.08 (dd, *J* = 9.3, 2.0 Hz, 1H), 2.17 – 2.11 (m, 1H), 2.08 – 1.92 (m, 1H), 1.82 – 1.61 (m, 7H), 1.54 – 1.44 (m, 2H), 1.36 (s, 3H), 1.30 (s, 3H), 0.82 (d, *J* = 4.9 Hz, 3H), 0.80 (d, *J* = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 130.4, 129.3, 126.2, 113.8, 100.0, 85.1, 72.8, 66.4, 65.2, 64.1, 61.2, 55.3, 41.0, 38.6, 36.2, 36.0, 35.9, 25.2, 25.0, 18.0, 12.3, 10.0. HRMS calc *m/z* $[C_{26}H_{42}O_5 + Na]^+$: 457.2924, found: 457.2897 and 417.2601 (hydrolyzed acetonide).



4.16b

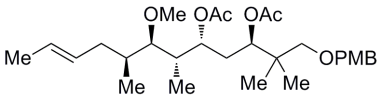
(*4R,6R*)-4-((*2S,3R,4S,E*)-3-Methoxy-4-methyloct-6-en-2-yl)-6-(1-((4-

methoxybenzyl)oxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxane (4.16b). To a solution of ester **4.15b** (8.8 mg, 0.019 mmol) in methanol (0.8 mL) was added potassium hydroxide (3.5 mg, 0.063 mmol). After stirring at room temperature for 8 h, additional potassium hydroxide (3.5 mg, 0.063 mmol) was added to the reaction. After stirring at room temperature overnight, the reaction was poured into saturated aqueous NH_4Cl. The mixture was extracted four times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was dissolved in 2,2-dimethoxypropane (1 mL) and PPTS (1 mg, 0.004 mmol) was added to the reaction. After stirring overnight at room temperature, the reaction was diluted with DCM and saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (5% EtOAc in hexanes) to yield 5.1 mg of product as a colorless oil (58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 6.92 – 6.84 (m, 2H), 5.51 – 5.36 (m, 2H), 4.50 – 4.35 (m, 2H), 4.03 (ddd, *J* = 9.2, 6.7, 2.4 Hz, 1H), 3.80 (s, 3H), 3.71 (dd, *J* = 10.6, 5.9 Hz, 1H), 3.46 (s, 3H), 3.30 – 3.10 (m, 2H), 3.08 (dd, *J* = 9.2, 1.9 Hz, 1H), 2.24 – 2.09 (m, 1H), 2.08 – 1.91 (m, 1H), 1.73 – 1.59 (m, 5H), 1.55 – 1.43 (m, 2H), 1.32 (s, 3H), 1.28 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). HRMS calc *m*/*z* $[C_{28}H_{46}O_5 + Na]^+$: 485.3237, found: 485.3220.



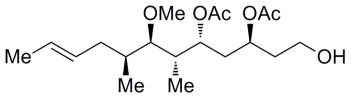
4.17a

(*3S,5R,6S,7R,8S,E*)-7-Methoxy-1-((4-methoxybenzyl)oxy)-6,8-dimethyldodec-10-ene-3,5-diyl Diacetate (4.17a). To solution of alcohol **4.15a** (53 mg, 0.12 mmol) in DCM (0.9 mL) was added TEA (0.30 mL, 2.2 mmol), Ac_2O (0.2 mL, 2.2 mmol) followed by DMAP (1 mg). The reaction was stirred overnight. The reaction was diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The biphasic mixture was stirred for 2.5 h. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (20% EtOAc in hexanes) to yield 46.1 mg of product as a colorless oil (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 4H), 6.94 – 6.79 (m, 2H), 5.55 – 5.34 (m, 2H), 5.30 (ddd, *J* = 9.2, 4.3, 2.1 Hz, 1H), 4.99 (dd, *J* = 10.0, 5.8 Hz, 1H), 4.40 (s, 2H), 3.80 (s, 3H), 3.54 – 3.45 (m, 2H), 3.43 (s, 3H), 2.84 (dd, *J* = 9.3, 2.3 Hz, 1H), 2.18 – 2.06 (m, 1H), 2.03 (s, 3H), 2.07 – 1.95 (m, 1H , 2.00 (s, 3H), 1.97 – 1.81 (m, 3H), 1.75 (ddd, *J* = 14.2, 9.7, 4.3 Hz, 1H), 1.70 – 1.58 (m, 5H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 159.1, 130.5, 130.1, 129.3, 126.4, 113.7, 85.3, 72.6, 69.9, 68.7, 66.3, 61.2, 55.2, 40.3, 38.4, 37.9, 35.8, 34.7, 21.1, 21.1, 18.0, 12.4, 10.6. HRMS calc *m/z* $[C_{27}H_{42}O_7 + Na]^+$: 501.2823, found: 501.2834.



4.17b

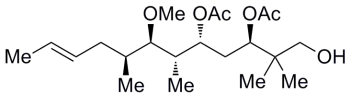
(*3R,5R,6S,7R,8S,E*)-7-Methoxy-1-((4-methoxybenzyl)oxy)-2,2,6,8-tetramethyldodec-10-ene-3,5-diyl Diacetate (4.17b). The product was synthesized following the procedure for the synthesis of intermediate **4.17a**. Reaction with alcohol **4.15b** (49.8 mg, 0.107 mmol) yielded 53.8 mg of product as a colorless oil (99% yield) following purification via silica gel flash chromatography (12% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 3H), 6.93 – 6.82 (m, 2H), 5.53 – 5.31 (m, 2H), 5.15 (dt, *J* = 10.1, 3.0 Hz, 1H), 5.01 (dd, *J* = 11.2, 2.4 Hz, 1H), 4.49 – 4.32 (ABq, 2H), 3.80 (s, 3H), 3.47 (s, 3H), 3.27 – 3.04 (ABq, 2H), 2.91 (dd, *J* = 9.3, 2.1 Hz, 1H), 2.21 – 2.07 (m, 1H), 2.04 (s, 3H), 2.00 (s, 3H), 1.99 – 1.85 (m, 2H), 1.77 – 1.59 (m, 6H), 0.93 (s, 3H), 0.88 (s, 3H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H). HRMS calc *m/z* $[C_{29}H_{46}O_7 + Na]^+$: 529.3136, found: 529.3120.



4.18a

(*3S,5R,6S,7R,8S,E*)-1-Hydroxy-7-methoxy-6,8-dimethyldodec-10-ene-3,5-diyl Diacetate (4.18a). To a solution of ester **4.17a** (46.1 mg, 0.0963 mmol) in DCM (1 mL) and water (0.09 mL) was added DDQ (55 mg, 0.24 mmol). After stirring at room temperature for 30 min, the reaction was diluted with DCM and quenched with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phase was washed with brine. The resulting emulsion was filtered through Celite® and the organic layer was separated and dried with

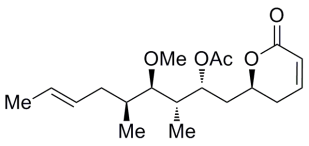
anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (20% EtOAc in hexanes and then 40% EtOAc in hexanes) to yield 21.5 mg of product as a colorless oil (62% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 5.61 (ddd, *J* = 9.9, 4.0, 2.1 Hz, 1H), 5.52 – 5.35 (m, 2H), 5.18 (tt, *J* = 9.9, 3.5 Hz, 1H), 3.61 – 3.49 (m, 1H), 3.49 – 3.40 (m, 1H), 3.46 (s, 3H), 2.88 (dd, *J* = 9.1, 2.4 Hz, 1H), 2.51 (bs, 1H), 2.25 – 2.11 (m, 1H), 2.12 – 1.96 (m, 1H), 1.87 (s, 3H), 1.75 (s, 3H), 1.72 – 1.52 (m, 8H), 1.45 (ddt, *J* = 13.7, 9.4, 4.0 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 171.9, 170.2, 130.7, 126.7, 85.6, 69.6, 68.0, 61.2, 58.3, 40.8, 38.9, 38.9, 38.5, 36.4, 20.9, 20.7, 18.2, 12.9, 10.9. HRMS calc *m/z* [$C_{19}H_{34}O_6$ + Na]$^+$: 381.2248, found: 381.2266.



4.18b

(*3R,5R,6S,7R,8S,E*)-1-Hydroxy-7-methoxy-2,2,6,8-tetramethyldodec-10-ene-3,5-diyl Diacetate (4.18b). The product was synthesized following the procedure for intermediate **4.18a**. Reaction with ether **4.17b** (20.1 mg, 0.0397 mmol) in DCM (1 mL) and water (0.09 mL) yielded 10.4 mg of product as a colorless oil (68% yield) following purification via silica gel flash chromatography (25% EtOAc in hexanes). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.54 – 5.33 (m, 2H), 5.20 (dt, *J* = 9.5, 2.9 Hz, 1H), 4.80 (dd, *J* = 11.1, 2.5 Hz, 1H), 3.41 (s, 3H), 3.22 (dd, *J* = 11.8, 4.3 Hz, 1H), 3.02 (t, *J* = 11.0 Hz, 1H), 2.90 (dd, *J* = 10.2, 4.4 Hz, 1H), 2.84 (dd, *J* = 9.1, 2.3 Hz, 1H), 2.20 – 2.03 (m, 1H), 2.08 (s, 3H), 2.05 – 1.92 (m, 1H), 2.00 (s, 3H), 1.92 – 1.82 (m, 1H), 1.80 – 1.70 (m, 1H), 1.69 –

1.59 (m, 5H), 0.94 (s, 3H), 0.83 (d, J = 7.1 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H), 0.76 (s, 3H). HRMS calc m/z $[C_{21}H_{38}O_6 + Na]^+$: 409.2561, found: 409.2544.

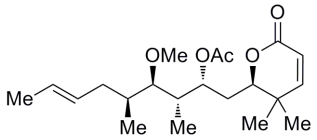


4.19a

(*2R,3S,4R,5S,E*)-4-Methoxy-3,5-dimethyl-1-((*S*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)non-7-en-2-yl Acetate (4.19a). A suspension of alcohol **4.18a** (21 mg, 0.059 mmol), NMO (10. mg, 0.088 mmol) and powdered 4Å molecular sieves (30 mg) was stirred in DCM (1 mL) at 0 °C for 15 min. A solution of TPAP (2 mg, 0.006 mmol) in DCM (0.2 mL) was added to the reaction. After stirring 40 min at 0 °C, the reaction was diluted with 40% EtOAc in hexanes and filtered through a plug of silica gel. The silica gel was rinsed with 40% EtOAc in hexanes. The crude aldehyde solution was concentrated using a rotary evaporator and the crude aldehyde was used without further purification.

To as solution of diisopropylamine (9.3 μL, 0.065 mmol) in THF (0.7 mL) at 0 °C was added *n*-butyllithium (2.4 M in hexanes, 25 μL, 0.060 mmol); the reaction was stirred at 0 °C for 20 min before cooling to -78 °C. Methyl acetate (5.2 μL, 0.065 mmol) was then added to reaction and the reaction was stirred at -78 °C for 40 min. A solution of the crude aldehyde dissolved in THF (0.24 mL) was added dropwise to the reaction. The vial containing the aldehyde solution was rinsed with additional THF (0.1 mL) and added dropwise to the reaction. The reaction was stirred at -78 °C for 1.5 h before warming to 0 °C and stirring for 30 min followed by warming to room temperature and stirring for an additional 15 min. The reaction was poured into DCM and pH 7 phosphate

buffer. The layers were separated and the aqueous phase was extracted three times with DCM and once with EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4% acetone in DCM) to yield 4.7 mg of product as a colorless oil (24% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 5.79 (ddd, *J* = 9.8, 6.0, 2.3 Hz, 1H), 5.68 (ddd, *J* = 9.8, 2.7, 0.9 Hz, 1H), 5.50 (td, *J* = 6.7, 2.1 Hz, 1H), 5.49 – 5.35 (m, 2H), 4.14 – 3.95 (m, 1H), 3.38 (s, 3H), 2.91 (dd, *J* = 9.3, 2.3 Hz, 1H), 2.22 – 2.11 (m, 1H), 2.13 – 1.99 (m, 1H), 1.89 – 1.62 (m, 5H), 1.73 (s, 3H), 1.62 (d, *J* = 4.3 Hz, 3H), 1.43 (dddd, *J* = 18.1, 6.0, 4.0, 0.7 Hz, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 170.0, 162.7, 143.7, 130.6, 126.6, 121.5, 85.5, 74.8, 70.6, 61.3, 39.7, 38.8, 38.2, 36.3, 29.1, 20.8, 18.1, 12.8, 10.6. HRMS calc *m/z* $[C_{19}H_{30}O_5 + Na]^+$: 361.1991, found: 361.1995.



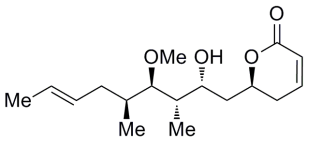
4.19b

***(2R,3S,4R,5S,E)*-1-((*R*)-3,3-Dimethyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-4-methoxy-3,5-dimethylnon-7-en-2-yl Acetate (4.19b)**. To a solution of alcohol **4.18b** (26.5 mg, 0.0686 mmol) in DCM (1 mL) was added Dess-Martin periodinane (0.3 M in DCM, 0.47 mL, 0.14 mmol) at room temperature. After 2 h, the reaction was quenched with a 1:1 mixture of saturated aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$ and stirred at room temperature for 30 min. The layers were separated and the aqueous phase was extracted

three times with DCM. The combined organic layers were washed with brine and dried with Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude aldehyde was used without further purification.

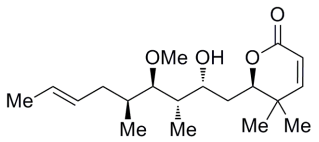
Lithium bis(trimethylsilyl)amide (1 M in hexanes, 72 μL, 0.072 mmol) was added to THF (0.7 mL) at room temperature and the solution was cooled to -78 °C. Methyl acetate (0.75 M in THF, 0.10 mL, 0.075 mmol) was then added to the reaction and the reaction was stirred at -78 °C for 20 min. A solution of the crude aldehyde dissolved in THF (0.2 mL) was then added dropwise to the reaction. The vial containing the aldehyde solution was rinsed with additional THF (0.1 mL) and added dropwise to the reaction. The reaction was stirred at -78 °C for 20 min before warming to 0 °C and stirring for 30 min followed by warming to room temperature and stirring for an additional 30 min. The reaction was poured into DCM and pH 7 phosphate buffer. The layers were separated and the aqueous phase was extracted three times with DCM and once with EtOAc. The combined organic layers were washed with brine and filtered through a plug of Celite®. The organic layer was dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (30% EtOAc in hexanes) to yield 13.1 mg of product as a colorless oil (52% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.60 (d, J = 9.7 Hz, 1H), 5.82 (d, J = 9.7 Hz, 1H), 5.55 – 5.39 (m, 2H), 5.37 (ddd, J = 7.3, 4.7, 2.4 Hz, 1H), 4.13 (dd, J = 9.2, 2.5 Hz, 1H), 3.38 (s, 3H), 2.89 (dd, J = 9.2, 2.3 Hz, 1H), 2.22 – 2.09 (m, 1H), 2.03 (s, 3H), 2.03 – 1.93 (m, 1H), 1.91 – 1.72 (m, 3H), 1.73 –

1.62 (m, 4H), 1.07 (s, 3H), 1.00 (s, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H). HRMS calc m/z $[C_{21}H_{34}O_5 + Na]^+$: 389.2298, found: 389.2298.



4.6a

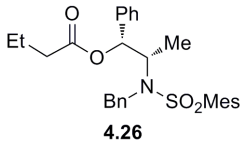
(*S*)-6-((*2R,3S,4R,5S,E*)-2-Hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (4.6a). To a solution of lactone **4.19a** (4.0 mg, 12 μmol) in MeOH (0.27 mL) was added HCl (3 M in MeOH, 50 μL, 150 μmol). The reaction was heated to 60 °C and stirred overnight. The reaction was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ and extracted four times with DCM and once with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude mixture was purified via silica gel flash chromatography (5% to 15% EtOAc in DCM) to yield 0.80 mg of product as a colorless oil (23% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 5.87 (ddd, J = 9.8, 5.8, 2.6 Hz, 1H), 5.82 – 5.62 (m, 1H), 5.58 – 5.26 (m, 2H), 4.43 (ddt, J = 11.3, 8.4, 4.1 Hz, 1H), 4.35 (dq, J = 9.6, 2.5 Hz, 1H), 3.10 (s, 3H), 3.04 (dd, J = 2.8, 1.1 Hz, 1H), 2.75 (dd, J = 6.4, 4.5 Hz, 1H), 2.12 – 1.97 (m, 1H), 1.87 – 1.69 (m, 2H), 1.69 – 1.50 (m, 5H), 1.50 – 1.40 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H). ^{13}C NMR (226 MHz, C_6D_6) δ 163.2, 144.1, 129.5, 128.0, 126.9, 121.7, 90.9, 75.1, 67.2, 61.1, 41.0, 39.4, 37.6, 36.6, 30.1, 18.2, 15.4, 11.9. HRMS calc m/z $[C_{17}H_{28}O_4 + Na]^+$: 319.1880, found: 319.1858. 96% pure by HPLC analysis.



4.6b

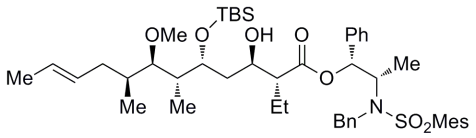
(*R*)-6-((*2R,3S,4R,5S,E*)-2-Hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,5-dimethyl-5,6-dihydro-2*H*-pyran-2-one (4.6b). To a solution of lactone **4.19b** (12.8 mg, 34.9 μmol) in MeOH (0.3 mL) was added HCl (3 M in MeOH, 60 μL, 180 μmol). The reaction was heated to 60 °C and stirred overnight to dryness. The reaction was cooled to room temperature and diluted with MeOH and quenched with saturated aqueous $NaHCO_3$ and extracted four times with DCM and once with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The crude ^{1}H NMR spectrum showed ~50% conversion, and the crude material was resubmitted to the reaction conditions and heated for an additional 26 h. The reaction was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ and extracted four times with DCM and once with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude mixture was purified via silica gel flash chromatography (5% to 15% EtOAc in hexanes) to yield 6.69 mg of product as a white solid (59% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.63 (d, *J* = 9.7 Hz, 1H), 5.82 (d, *J* = 9.7 Hz, 1H), 5.56 – 5.35 (m, 2H), 4.40 (dd, *J* = 10.6, 1.7 Hz, 1H), 4.17 (dd, *J* = 9.9, 2.4 Hz, 1H), 3.47 (s, 3H), 3.18 (d, *J* = 3.4 Hz, 1H), 3.01 (t, *J* = 5.4 Hz, 1H), 2.20 – 2.07 (m, 1H), 1.97 – 1.75 (m, 3H), 1.73 – 1.59 (m, 5H), 1.53 (ddd, *J* = 13.9, 10.6, 2.5 Hz, 1H), 1.10 (s, 3H), 1.02 (s, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, CD_2Cl_2) δ 164.7, 157.6, 129.7, 127.3, 119.0, 91.2, 82.3, 67.5, 61.9, 39.7, 37.8, 36.8, 35.3, 35.0, 24.9, 19.9, 18.3, 15.3, 12.4. HRMS calc *m/z* [$C_{19}H_{32}O_4$ + Na]$^+$: 347.2193, found: 347.2199. 97% pure by HPLC analysis.



4.26

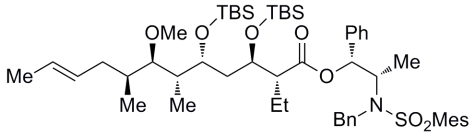
(1*R*,2*S*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl Butyrate (4.26). To a solution of (*1R,2S*)-2-[*N*-Benzyl-*N*-(mesitylenesulfonyl)amino]-1-phenyl-1-propanol (0.35 g, 0.83 mmol) and pyridine (0.087 mL, 1.1 mmol) in DCM (4.7 mL) at 0 °C was added butyryl chloride (0.10 mL, 0.99 mmol) dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was diluted with ether and washed with water, 1 M HCl, saturated aqueous $NaHCO_3$, and brine before drying with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (70% DCM in hexanes) to yield 0.64 g of product as a white solid (77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H), 7.29 – 7.14 (m, 4H), 6.95 – 6.83 (m, 4H), 5.82 (d, *J* = 4.1 Hz, 1H), 4.84 – 4.50 (m, 2H), 4.05 (qd, *J* = 6.9, 4.1 Hz, 1H), 2.51 (s, 6H), 2.28 (s, 3H), 2.22 – 2.01 (m, 2H), 1.54 (h, *J* = 7.8 Hz, 4H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 142.5, 140.2, 138.7, 138.6, 133.4, 132.1, 128.4, 128.3, 127.8, 127.4, 127.1, 126.0, 77.9, 56.7, 48.1, 36.1, 23.0, 20.9, 18.1, 13.6, 12.9. $[\alpha]_D$ = +17.5 (*c* 0.189, $CHCl_3$). HRMS calc *m/z* [$C_{29}H_{35}NO_4S$ + Na]$^+$: 516.2179, found: 516.2132. mp: 79.2 – 80.4 °C.



4.27

(1*R*,2*S*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl (2*R*,3*R*,5*R*,6*R*,7*R*,8*S*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-ethyl-3-hydroxy-7-methoxy-6,8-dimethyldodec-10-enoate (4.27). Ester **4.26** (74 mg, 0.15 mmol) was dissolved in DCM (2 mL) and cooled to -78 °C. A solution of TEA (84 µL, 0.60 mmol) and dicyclohexylboron trifluoromethanesulfonate (98 mg, 0.30 mmol) in DCM (0.4 mL) cooled to -78 °C was transferred dropwise via cannula to the reaction and the reaction was stirred at -78 °C for 2 h. A solution of aldehyde **4.25** (42.9 mg, 0.125 mmol) in DCM (0.2 mL) was added dropwise to the reaction. The vial containing the aldehyde solution was rinsed with additional DCM (0.2 mL) which was added to the reaction. The reaction was stirred at -78 °C for 2 h before warming to -40 °C and stirring overnight. The reaction was warmed to 0 °C and stirred for 1 h. The reaction was quenched with MeOH (0.7 mL), pH 7 phosphate buffer (0.7 mL), and 30% hydrogen peroxide (0.7 mL) and vigorously stirred at room temperature for 8 h. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and the volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (10% EtOAc in hexanes followed by 100:1 to 100:1.5 DCM:acetone) to yield 58.2 mg of product as a colorless oil (56% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.61 – 7.46 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 2H), 7.06 – 6.94 (m, 6H), 6.51 (s, 2H), 6.20 (d, *J* = 5.3 Hz, 1H), 5.58 – 5.34 (ABq, 2H), 4.85

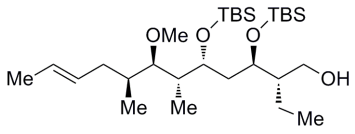
(dd, *J* = 138.9, 16.4 Hz, 2H), 4.51 – 4.32 (m, 2H), 4.10 (dtd, *J* = 9.2, 6.4, 2.4 Hz, 1H), 3.37 (s, 3H), 3.19 (dd, *J* = 8.7, 2.0 Hz, 1H), 2.90 (d, *J* = 6.2 Hz, 1H), 2.53 (s, 6H), 2.38 (dt, *J* = 8.7, 6.0 Hz, 1H), 2.30 – 2.17 (m, 1H), 2.14 – 2.00 (m, 1H), 1.94 – 1.84 (m, 1H), 1.88 (s, 3H), 1.78 (ddd, *J* = 14.1, 6.5, 2.6 Hz, 1H), 1.69 (qd, *J* = 6.6, 1.6 Hz, 1H), 1.64 (d, *J* = 4.5 Hz, 3H), 1.62 – 1.44 (m, 3H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.03 – 0.96 (m, 12H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.72 (t, *J* = 7.4 Hz, 3H), 0.19 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 174.0, 142.1, 140.6, 139.5, 139.0, 134.5, 132.3, 130.9, 128.6, 128.5, 127.4, 127.1, 126.6, 84.6, 78.5, 70.9, 69.8, 60.4, 57.1, 54.3, 48.7, 42.2, 42.1, 39.0, 36.1, 26.3, 23.2, 22.9, 20.6, 18.6, 18.2, 14.7, 13.6, 11.9, 11.4, -3.6, -3.8. HRMS calc *m*/*z* $[C_{48}H_{73}NO_7SSi + Na]^+$: 858.4775, found: 858.4855.



4.28

(1*R*,2*S*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl (2*R*,3*R*,5*R*,6*R*,7*R*,8*S*,*E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-enoate (4.28). To a solution of alcohol **4.27** (51.6 mg, 0.0617 mmol) in DCM (1 mL) was added 2,6-lutidine (30 µL, 0.26 mmol) followed by TBSOTf (25 µL, 0.11 mmol) dropwise. The reaction was warmed to room temperature and stirred for 1 h and then quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (5% EtOAc in hexanes) to yield

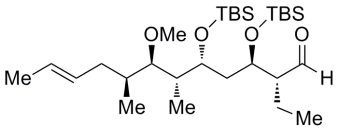
52.7 mg of product as a colorless oil (90% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.56 – 7.43 (m, 2H), 7.24 – 7.13 (m, 3H), 7.13 – 6.93 (m, 6H), 6.51 (s, 2H), 6.18 (d, *J* = 5.5 Hz, 1H), 5.56 – 5.34 (m, 2H), 5.11 – 4.52 (m, 2H), 4.51 – 4.35 (m, 2H), 4.07 – 3.91 (m, 1H), 3.49 (s, 3H), 3.30 (dd, *J* = 9.7, 1.6 Hz, 1H), 2.61 (td, *J* = 7.2, 2.5 Hz, 1H), 2.50 (s, 6H), 2.33 – 2.18 (m, 1H), 2.18 – 2.02 (m, 1H), 1.92 (s, 3H), 1.99 – 1.86 (m, 2H), 1.86 – 1.77 (m, 1H), 1.78 – 1.54 (m, 6H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.03 – 0.95 (m, 22H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 171.5, 142.0, 140.5, 139.5, 139.2, 134.4, 132.3, 131.0, 128.6, 128.4, 128.4, 127.9, 127.4, 127.2, 126.5, 83.8, 79.1, 70.5, 69.2, 61.4, 57.5, 52.7, 48.7, 41.1, 40.2, 38.7, 36.1, 26.3, 26.1, 23.2, 21.4, 20.6, 18.5, 18.4, 18.2, 15.2, 12.9, 12.3, 9.4, -2.8, -3.9, -4.5, -4.5. HRMS calc *m/z* $[C_{54}H_{87}NO_7SSi_2 + Na]^+$: 972.5639, found: 972.5743.



4.29

(*2S,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-en-1-ol (4.29). To a solution of ester **4.28** (52.4 mg, 0.0551 mmol) dissolved in DCM (1 mL) at -78 °C was added DIBAL-H (1 M in hexanes, 0.17 mL, 0.17 mmol). The reaction was stirred at -78 °C for 2.5 h before additional DIBAL-H (1 M in hexanes, 0.17 mL, 0.17 mmol) was added to the reaction. The reaction was quenched with MeOH (20 μL) followed by saturated aqueous Rochelle salt and warmed to room temperature. After stirring for 2 h, the layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phase was washed with brine

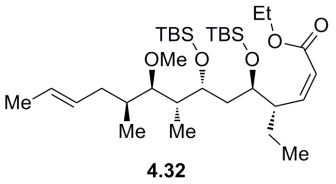
and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and purified via silica gel flash chromatography (11:1 hexanes:EtOAc) to yield 21.2 mg of product as a colorless oil (72% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 5.57 – 5.34 (m, 2H), 4.24 (dd, *J* = 10.5, 4.5 Hz, 1H), 4.21 – 4.05 (m, 1H), 4.07 – 3.94 (m, 1H), 3.81 (ddd, *J* = 11.5, 8.1, 4.5 Hz, 1H), 3.40 (s, 3H), 3.27 (dd, *J* = 9.8, 1.7 Hz, 1H), 2.55 (d, *J* = 8.0 Hz, 1H), 2.23 (ddd, *J* = 13.4, 10.1, 4.9 Hz, 2H), 2.15 – 2.06 (m, 1H), 2.01 (ddd, *J* = 13.4, 10.6, 4.7 Hz, 1H), 1.80 – 1.53 (m, 8H), 1.05 – 0.99 (m, 12H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.21 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 130.9, 126.5, 84.0, 72.9, 69.0, 62.4, 61.1, 44.6, 41.4, 40.0, 38.8, 36.1, 26.2, 26.0, 22.2, 18.5, 18.2, 18.1, 12.8, 12.4, 9.5, -2.8, -4.1, -4.3, -4.7. HRMS calc *m/z* $[C_{29}H_{62}O_4Si_2 + Na]^+$: 553.4079, found: 553.4098.



4.30

(*2R,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-enal (4.30). A suspension of alcohol **4.29** (21.2 mg, 0.0399 mmol), NMO (6.1 mg, 0.052 mmol), and powdered 4Å molecular sieves (20 mg) was stirred in DCM (0.6 mL) at 0 °C for 15 min. A solution of TPAP (1.4 mg, 0.0040 mmol) in DCM (0.2 mL) was added to the reaction. After stirring 20 min at 0 °C, the reaction was warmed to room temperature and stirred for 30 min. Silica gel was added to the reaction and volatile materials were removed using a rotary evaporator. Purification via silica gel flash chromatography yielded 17.9 mg of product as a colorless oil (85% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 9.83 (d, *J* = 3.6 Hz, 1H), 5.55 – 5.28 (m, 2H), 4.40 (dd, *J* = 9.4,

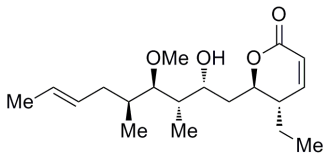
5.6 Hz, 1H), 3.95 (ddd, *J* = 8.6, 5.9, 1.8 Hz, 1H), 3.47 (s, 3H), 3.28 (dd, *J* = 9.8, 1.7 Hz, 1H), 2.29 (dddd, *J* = 8.1, 6.1, 3.7, 1.9 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.15 – 2.06 (m, 1H), 2.06 – 1.97 (m, 2H), 1.83 – 1.68 (m, 2H), 1.68 – 1.62 (m, 3H), 1.62 – 1.46 (m, 2H), 1.00 (s, 9H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.26 (s, 3H), 0.24 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 204.3, 130.9, 126.6, 83.9, 71.2, 68.6, 61.3, 56.9, 42.2, 40.4, 38.7, 36.1, 26.2, 25.9, 20.1, 18.5, 18.2, 12.9, 11.9, 9.4, -2.9, -4.1, -4.4, -4.7. HRMS calc *m/z* [$C_{29}H_{60}O_4Si_2$ + K]$^+$: 567.3662, found: 567.3780.



4.32

(*2Z,4S,5R,7R,8R,9R,10S,12E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-4-ethyl-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (4.32). To a solution of phosphonate ester **4.31** (121 mg, 0.347 mmol) in THF (4.3 mL) at 0 °C was added sodium hydride (60% in mineral oil, 14 mg, 0.35 mmol). The reaction was stirred at 0 °C for 15 min before cooling to -78 °C. Aldehyde **4.30** (17.9 mg, 0.0338 mmol) was dissolved in THF (0.3 mL) and added to the reaction dropwise. The vial containing the aldehyde solution was rinsed with additional THF (0.3 mL) which was added to the reaction. The reaction was slowly warmed from -78 °C to ~0 °C over 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and

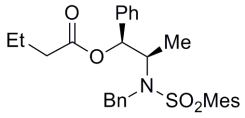
volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4% ether in hexanes and 5% ether in hexanes) to yield 11.5 mg of product as a colorless oil (57% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 6.47 (dd, *J* = 11.7, 10.2 Hz, 1H), 6.04 (d, *J* = 11.6 Hz, 1H), 5.52 – 5.37 (m, 2H), 4.38 (dd, *J* = 9.2, 5.2 Hz, 1H), 4.14 – 3.95 (m, 3H), 3.96 – 3.84 (m, 1H), 3.62 (s, 3H), 3.33 (dd, *J* = 9.6, 1.8 Hz, 1H), 2.39 – 2.24 (m, 1H), 2.17 – 2.06 (m, 1H), 2.00 – 1.84 (m, 2H), 1.84 – 1.72 (m, 2H), 1.73 – 1.62 (m, 4H), 1.63 – 1.45 (m, 2H), 1.07 – 0.98 (m, 9H), 1.02, (s, 9H), 0.99 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 4H), 0.20 (s, 6H), 0.19 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 166.0, 150.6, 131.1, 126.4, 121.7, 83.9, 71.3, 69.1, 61.3, 59.7, 44.0, 42.7, 40.8, 38.9, 36.2, 26.3, 26.1, 25.2, 18.6, 18.3, 18.2, 14.3, 13.0, 12.1, 9.6, -2.8, -3.9, -4.2, -4.4. HRMS calc *m/z* $[C_{33}H_{66}O_5Si_2 + Na]^+$: 621.4347, found: 621.4364.



4.20

(*5S,6R*)-5-Ethyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (4.20). Ester **4.32** (11.5 mg, 0.0192 mmol) was dissolved in a hydrochloric acid/ethanol solution (1% HCl in ethanol, 0.48 mL) and stirred at room temperature overnight. The reaction was diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phase was washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was

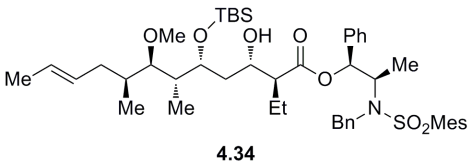
purified via silica gel flash chromatography (5% EtOAc in DCM and 35% EtOAc in hexanes twice) to yield 8.48 mg of product as a colorless oil (44% yield).) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 9.9, 3.5 Hz, 1H), 6.00 (dd, *J* = 9.8, 2.0 Hz, 1H), 5.56 – 5.29 (m, 2H), 4.54 (ddd, *J* = 9.9, 7.5, 2.9 Hz, 1H), 4.24 (dq, *J* = 10.0, 2.6 Hz, 1H), 3.47 (s, 3H), 3.38 (dd, *J* = 3.2, 1.1 Hz, 1H), 2.98 (dd, *J* = 6.1, 4.6 Hz, 1H), 2.31 (tdt, *J* = 7.7, 5.2, 2.0 Hz, 1H), 2.19 – 2.01 (m, 1H), 1.94 – 1.72 (m, 4H), 1.72 – 1.61 (m, 4H), 1.50 (dt, *J* = 13.8, 7.4 Hz, 1H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 149.1, 128.8, 126.9, 120.6, 90.8, 78.9, 67.4, 61.5, 39.8, 39.0, 38.7, 37.3, 36.1, 24.3, 18.0, 15.1, 12.2, 10.6. HRMS calc *m/z* $[C_{19}H_{32}O_4 + Na]^+$: 347.2193, found: 347.2201. 97% pure by HPLC analysis.



4.33

(1*S*,2*R*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl Butyrate (4.33). The product was synthesized following the procedure for the synthesis of ester **4.26**. Reaction with (*1S,2R*)-2-[*N*-benzyl-*N*-(mesitylenesulfonyl)amino]-1-phenyl-1-propanol (0.35 g, 0.83 mmol) resulted in 0.32 g of product as a white solid (77% yield) after purification via silica gel flash chromatography (70% DCM in hexanes and 0.5% ether in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.1 Hz, 2H), 7.29 – 7.12 (m, 4H), 6.96 – 6.81 (m, 4H), 5.82 (d, *J* = 4.0 Hz, 1H), 4.85 – 4.51 (ABq, 2H), 4.05 (qd, *J* = 7.0, 4.0 Hz, 1H), 2.51 (s, 6H), 2.28 (s, 3H), 2.26 – 1.97 (m, 2H), 1.54 (d, *J* = 7.6 Hz, 2H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 142.5, 140.2, 138.7, 138.6, 133.4, 132.1, 128.4, 128.3, 127.8, 127.4, 127.1, 126.0, 77.9,

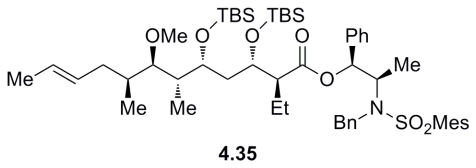
56.7, 48.2, 36.1, 23.0, 20.9, 18.1, 13.6, 12.9. $[\alpha]_D$ = -17.5 (*c* 0.188, $CHCl_3$). HRMS calc *m/z* $[C_{29}H_{35}NO_4S + Na]^+$: 516.2179, found: 516.2146. mp: 80.8 – 81.5 °C.



4.34

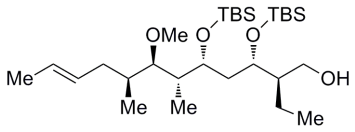
(1*S*,2*R*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl (2*S*,3*S*,5*R*,6*R*,7*R*,8*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-2-ethyl-3-hydroxy-7-methoxy-6,8-dimethyldodec-10-enoate (4.34). The product was synthesized following the procedure for the synthesis of intermediate **4.27.** Reaction with ester **4.33** (0.16 g, 0.33 mmol), TEA (0.18 mL, 1.3 mmol), dicyclohexylboron trifluoromethanesulfonate (0.22 g, 0.66 mmol) and aldehyde **4.25** (47.2 mg, 0.138 mmol) resulted in 76 mg of product as a colorless oil (66% yield) after purification via silica gel flash chromatography (25% ether in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 7.63 – 7.54 (m, 2H), 7.16 – 7.10 (m, 2H), 7.09 – 7.00 (m, 1H), 7.01 – 6.91 (m, 5H), 6.53 (s, 2H), 6.21 (d, *J* = 5.0 Hz, 1H), 5.55 – 5.35 (ABq, 2H), 5.13 – 4.68 (m, 2H), 4.49 (dd, *J* = 9.6, 4.3 Hz, 1H), 4.38 (td, *J* = 7.0, 5.1 Hz, 1H), 3.92 (s, 1H), 3.39 (s, 3H), 3.26 (dd, *J* = 9.5, 1.8 Hz, 1H), 2.97 (d, *J* = 5.4 Hz, 1H), 2.54 (s, 6H), 2.42 (ddd, *J* = 9.5, 7.3, 4.6 Hz, 1H), 2.30 – 2.16 (m, 1H), 2.15 – 2.02 (m, 1H), 1.89 (s, 3H), 1.88 – 1.68 (m, 4H), 1.65 (d, *J* = 4.2 Hz, 3H), 1.61 – 1.48 (m, 1H), 1.50 – 1.39 (m, 1H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.64 (t, *J* = 7.4 Hz, 3H), 0.23 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 174.1, 142.1, 140.6, 139.8, 139.1, 134.6, 132.3, 130.9, 128.6, 128.5, 128.4, 127.4, 127.0, 126.5, 84.8, 78.4, 70.0, 69.7, 60.9, 57.2, 54.5,

48.6, 41.5, 40.1, 38.8, 36.1, 26.2, 23.2, 22.6, 20.6, 18.5, 18.2, 14.6, 13.1, 11.8, 10.1, -3.1, -4.1. HRMS calc *m/z* $[C_{48}H_{73}NO_7SSi + Na]^+$: 858.4775, found: 858.4813.



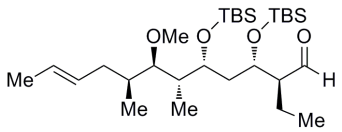
4.35

(1*S*,2*R*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl (2*S*,3*S*,5*R*,6*R*,7*R*,8*S*,*E*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-enoate (4.35). The product was synthesized following the procedure for the synthesis of intermediate **4.28.** Reaction with alcohol **4.34** (0.103 g, 0.123 mmol) resulted in 99 mg of product as a colorless oil (85% yield) after purification via silica gel flash chromatography (5% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 7.55 – 7.46 (m, 2H), 7.14 – 7.06 (m, 2H), 7.05 – 7.00 (m, 1H), 7.00 – 6.90 (m, 5H), 6.47 (s, 2H), 6.13 (d, *J* = 6.7 Hz, 1H), 5.44 (dq, *J* = 4.7, 2.0 Hz, 2H), 5.01 – 4.41 (ABq, 2H), 4.51 – 4.30 (m, 2H), 4.19 (dt, *J* = 9.9, 2.7 Hz, 1H), 3.46 (s, 3H), 3.32 (dd, *J* = 9.7, 1.6 Hz, 1H), 2.64 (dt, *J* = 8.6, 4.5 Hz, 1H), 2.45 (s, 6H), 2.33 – 2.21 (m, 1H), 2.17 – 2.04 (m, 1H), 1.97 – 1.80 (m, 4H), 1.89 (s, 3H), 1.80 – 1.69 (m, 2H), 1.69 – 1.59 (m, 3H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 18H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 4H), 0.71 (d, *J* = 6.8 Hz, 3H), 0.27 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 172.0, 142.0, 140.6, 139.0, 138.8, 134.1, 132.3, 131.2, 128.7, 128.5, 128.1, 127.6, 127.3, 126.3, 83.9, 78.1, 70.0, 69.1, 60.9, 56.9, 54.8, 48.7, 39.4, 38.9, 38.9, 36.2, 26.3, 26.2, 23.1, 20.6, 18.6, 18.5, 18.5, 18.2, 15.8, 13.3, 12.9, 9.4, -2.6, -4.0, -4.1, -4.6. HRMS calc *m/z* $[C_{54}H_{87}NO_7SSi_2 + Na]^+$: 972.5634, found: 972.5703.



4.36

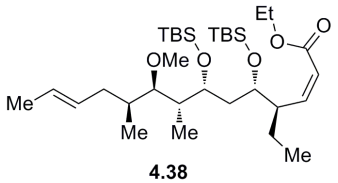
(*2R,3S,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-en-1-ol (4.36). The product was synthesized following the procedure for the synthesis of intermediate **4.29**. Reaction with ester **4.35** (97.9 mg, 0.103 mmol) resulted in 48.2 mg of product as a colorless oil (88% yield) after purification via silica gel flash chromatography (11:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, C_6D_6) δ 5.53 – 5.38 (m, 2H), 4.41 (dd, *J* = 8.9, 5.4 Hz, 1H), 4.06 (dt, *J* = 7.5, 3.7 Hz, 1H), 3.59 (dt, *J* = 10.9, 3.8 Hz, 1H), 3.47 (s, 3H), 3.39 – 3.28 (m, 2H), 2.36 – 2.21 (m, 1H), 2.21 – 2.03 (m, 1H), 1.91 – 1.75 (m, 4H), 1.75 – 1.60 (m, 4H), 1.55 (ddq, *J* = 11.5, 7.5, 3.8 Hz, 1H), 1.32 (ddt, *J* = 16.5, 14.4, 7.3 Hz, 1H), 1.22 (dd, *J* = 6.3, 3.6 Hz, 1H), 1.04 (s, 18H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.26 (s, 3H), 0.23 (s, 3H), 0.22 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 131.1, 126.4, 84.1, 71.4, 69.7, 62.6, 60.9, 48.3, 40.0, 39.5, 38.9, 36.3, 26.4, 26.2, 19.8, 18.6, 18.3, 18.2, 13.0, 12.9, 9.8, -2.7, -3.9, -4.0, -4.3. HRMS calc *m/z* $[C_{29}H_{62}O_4Si_2 + Na]^+$: 553.4084, found: 553.4170.



4.37

(*2S,3S,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-enal (4.37). The product was synthesized following the procedure for the synthesis of intermediate **4.30.** Reaction with alcohol **4.36** (42.1 mg, 0.0793 mmol)

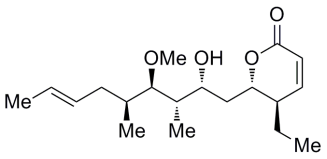
resulted in 36.0 mg of product as a colorless oil (86% yield) after purification via silica gel flash chromatography (5% EtOAc in hexanes) ^{1}H NMR (400 MHz, C_6D_6) δ 9.53 (d, *J* = 2.0 Hz, 1H), 5.56 – 5.32 (m, 2H), 4.39 (ddd, *J* = 10.0, 4.3, 1.2 Hz, 1H), 4.10 (dt, *J* = 8.6, 3.3 Hz, 1H), 3.45 (s, 3H), 3.30 (dd, *J* = 9.6, 1.7 Hz, 1H), 2.34 – 2.18 (m, 2H), 2.19 – 2.02 (m, 1H), 1.92 – 1.79 (m, 2H), 1.79 – 1.55 (m, 7H), 1.05 – 0.96 (m, 21H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.20 (s, 3H), 0.18 (s, 6H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.7, 131.1, 126.4, 84.0, 69.5, 69.2, 60.8, 60.0, 40.6, 39.8, 38.9, 36.2, 26.3, 26.1, 18.6, 18.2, 18.2, 17.8, 13.0, 12.8, 9.6, -2.7, -4.0, -4.2, -4.4. HRMS calc *m*/*z* $[C_{29}H_{60}O_4Si_2 + Na]^+$: 551.3928, found: 551.3856.



4.38

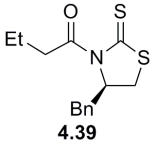
(*2Z,4R,5S,7R,8R,9R,10S,12E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-4-ethyl-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (4.38). The product was synthesized following the procedure for the synthesis of intermediate **4.32**. Reaction with aldehyde **4.37** (35.5 mg, 0.0671 mmol) resulted in 29.6 mg of product as a colorless oil (74% yield) after purification via silica gel flash chromatography (3% ether in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 5.96 – 5.84 (m, 2H), 5.53 – 5.38 (m, 2H), 4.47 (ddd, *J* = 9.2, 5.2, 1.4 Hz, 1H), 4.06 (dt, *J* = 8.5, 3.4 Hz, 1H), 4.02 – 3.83 (m, 3H), 3.49 (s, 3H), 3.33 (dd, *J* = 9.5, 1.7 Hz, 1H), 2.37 – 2.21 (m, 1H), 2.19 – 2.05 (m, 1H), 2.02 – 1.85 (m, 2H), 1.86 – 1.68 (m, 3H), 1.68 – 1.60 (m, 3H), 1.43 – 1.29 (m, 1H), 1.10 (s, 9H), 1.05 (s, 9H), 1.00 – 0.91 (m, 10H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.38 (s, 3H), 0.36 (s, 3H), 0.28 (s, 3H),

0.24 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 165.9, 151.5, 131.1, 126.4, 122.0, 83.8, 72.0, 69.7, 60.8, 59.8, 46.0, 40.4, 39.9, 38.9, 36.3, 26.4, 26.4, 22.9, 18.6, 18.4, 18.2, 14.2, 12.9, 12.6, 9.8, -2.7, -3.7, -3.8, -4.5. HRMS calc *m/z* $[C_{33}H_{66}O_5Si_2 + Na]^+$: 621.4341, found: 621.4409.



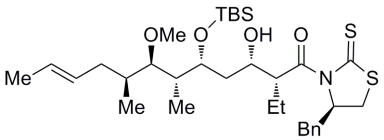
4.21

(*5R,6S*)-5-Ethyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (4.21). The product was synthesized following the procedure for the synthesis of analog **4.20**. Reaction with ester **4.38** (29.5 mg, 0.0492 mmol) resulted in 4.05 mg of product as a colorless oil (25% yield) after purification via silica gel flash chromatography (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 9.9, 3.5 Hz, 1H), 6.00 (dd, *J* = 9.9, 2.0 Hz, 1H), 5.53 – 5.29 (m, 2H), 4.45 (td, *J* = 7.4, 5.0 Hz, 1H), 4.25 – 4.13 (m, 1H), 3.49 (s, 3H), 3.23 (d, *J* = 2.7 Hz, 1H), 3.06 (t, *J* = 5.7 Hz, 1H), 2.45 (ddt, *J* = 9.8, 7.7, 4.0 Hz, 1H), 2.19 – 2.09 (m, 1H), 2.01 (ddd, *J* = 14.5, 8.8, 7.4 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.84 – 1.62 (m, 7H), 1.48 (dt, *J* = 14.3, 7.4 Hz, 1H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 149.2, 129.2, 126.8, 120.4, 89.2, 80.6, 68.1, 61.6, 39.4, 39.0, 38.0, 37.4, 36.0, 24.0, 18.0, 14.3, 11.3, 10.6. HRMS calc *m/z* $[C_{19}H_{32}O_4 + Na]^+$: 347.2193, found: 347.2170. 97% pure by HPLC analysis.



4.39

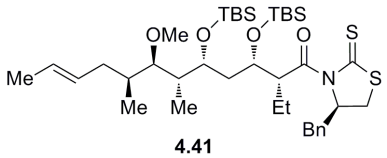
(*R*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)butan-1-one (4.39). To a solution of (*R*)-4-benzylthiazolidine-2-thione (0.25 g, 1.2 mmol) and triethylamine (0.18 mL, 1.3 mmol) in DCM (2 mL) at 0 °C was added dropwise a solution of butyryl chloride (0.13 mL, 1.25 mmol) dissolved in DMM (0.5 mL) over 7 min. The vial containing the butyryl chloride solution was rinsed with additional DCM (0.5 mL) which was added to the reaction. The reaction was warmed to room temperature and stirred for 2 h. The reaction was then quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The suspension was filter and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (1:1 DCM:hexanes) to yield 0.25 g of product as a yellow solid (75% yield). The resonances in the ^1H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[132]



4.40

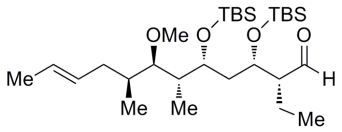
(*2R,3S,5R,6R,7R,8S,E*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-2-ethyl-3-hydroxy-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.40). The procedure was adapted from a previously reported reaction.[50] Thiazolidinethione **4.39** (115 mg, 0.412 mmol) was dissolved in DCM (1.7 mL) and cooled to 0 °C. Titanium chloride (45 µL, 0.41 mmol) was added to the reaction dropwise and the reaction was stirred for 20 min at 0 °C. Diisopropylethylamine (72 µL, 0.41 mmol) was added to the reaction dropwise and the reaction was stirred for an

additional 20 min at 0 °C before adding NMP (40 μL, 0.41 mmol) dropwise to the reaction. The reaction was stirred for an additional 20 min at 0 °C before cooling to -78 °C. Aldehyde **4.25** (41 mg, 0.12 mmol) was dissolved in DCM (0.5 mL) and added dropwise to the reaction at -78 °C. The vial containing the aldehyde solution was rinsed with additional DCM (0.5 mL) which was added to the reaction dropwise. The reaction was stirred at -78 °C for 4 h before warmed to -50 °C and stirring overnight. The reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4:1 hexanes:EtOAc) to yield 55.8 mg of product as a yellow oil (75% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.11 – 7.01 (m, 3H), 7.01 – 6.94 (m, 2H), 5.54 – 5.36 (m, 2H), 5.20 – 5.04 (m, 2H), 4.50 (ddd, *J* = 9.8, 4.1, 1.3 Hz, 1H), 3.97 (ddd, *J* = 10.5, 5.0, 2.3 Hz, 1H), 3.45 (s, 3H), 3.31 (dd, *J* = 9.5, 1.7 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.7 Hz, 1H), 2.70 (dd, *J* = 13.2, 10.6 Hz, 1H), 2.49 (dd, *J* = 11.5, 7.1 Hz, 1H), 2.33 – 2.17 (m, 1H), 2.17 – 1.94 (m, 4H), 1.94 – 1.81 (m, 2H), 1.80 – 1.67 (m, 2H), 1.67 – 1.59 (m, 3H), 1.08 – 0.97 (m, 15H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.26 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.2, 176.5, 137.0, 131.0, 129.6, 129.0, 127.2, 126.5, 84.5, 70.5, 69.9, 69.4, 61.0, 51.0, 40.4, 40.2, 38.9, 37.0, 36.2, 31.4, 26.3, 21.2, 18.6, 18.2, 13.2, 12.2, 10.0, -2.9, -4.2. HRMS calc *m/z* $[C_{33}H_{55}NO_4S_2Si + Na]^+$: 644.3234, found: 644.3206.



4.41

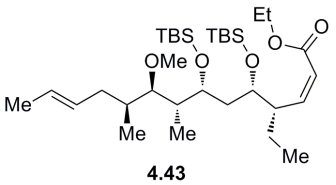
(*2R,3S,5R,6R,7R,8S,E*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.41). To a solution of alcohol **4.40** (55.8 mg, 0.0897 mmol) and 2,6-lutidine (21 µL, 0.18 mmol) in DCM (0.8 mL) at 0 °C was added TBSOTf (31 µL, 0.14 mmol) dropwise. The reaction was removed from the ice bath and stirred at room temperature. After 35 min, the reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extract three times with DCM. Wash combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4% EtOAc in hexanes) to yield 49.9 mg of product as a yellow oil (76% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.13 – 6.98 (m, 5H), 5.57 – 5.38 (m, 2H), 5.18 (ddd, *J* = 10.5, 6.9, 3.6 Hz, 1H), 4.92 (td, *J* = 7.0, 3.8 Hz, 1H), 4.50 (dd, *J* = 9.9, 4.6 Hz, 1H), 4.07 (dt, *J* = 7.2, 3.2 Hz, 1H), 3.49 (s, 3H), 3.37 (dd, *J* = 9.8, 1.6 Hz, 1H), 3.20 (dd, *J* = 13.1, 3.6 Hz, 1H), 2.86 – 2.69 (m, 2H), 2.36 – 2.22 (m, 3H), 2.21 – 2.09 (m, 3H), 1.92 – 1.76 (m, 2H), 1.76 – 1.56 (m, 4H), 1.13 – 0.98 (m, 24H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.35 (s, 3H), 0.29 (s, 3H), 0.25 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 201.4, 175.4, 137.1, 131.1, 129.7, 129.0, 127.2, 126.4, 84.1, 71.1, 69.6, 69.2, 60.9, 52.3, 41.0, 39.5, 38.9, 36.8, 36.2, 31.6, 26.4, 26.3, 22.0, 18.7, 18.3, 18.2, 12.9, 11.9, 9.5, -2.3, -3.8, -3.9, -4.2. HRMS calc *m/z* $[C_{39}H_{69}NO_4S_2Si_2 + Na]^+$: 758.4104, found: 758.4091.



4.42

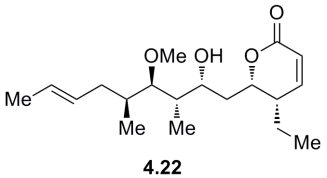
(*2R,3S,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-enal (4.42). To a solution of amide **4.41** (49.9 mg, 0.0678 mmol) in DCM (1.6 mL) at -78 °C was added DIBAL-H (1 M in hexanes, 0.14 mL, 0.14 mmol) dropwise. The yellow color persisted after 5 min and additional DIBAL-H (1 M in hexanes, 0.07 mL, 0.07 mmol) was added dropwise to the reaction. After stirring an additional couple min, the reaction was quenched with saturated aqueous Rochelle salt and diluted with DCM and warmed to room temperature. The slurry was stirred at room temperature for 1.5 h. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4% EtOAc in hexanes) to yield 28.6 mg of product as a white solid (80% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 9.93 (d, *J* = 1.8 Hz, 1H), 5.54 – 5.35 (m, 2H), 4.39 (dd, *J* = 8.7, 5.1 Hz, 1H), 3.96 (dt, *J* = 8.2, 4.2 Hz, 1H), 3.44 (s, 3H), 3.31 (dd, *J* = 9.7, 1.6 Hz, 1H), 2.32 (dtd, *J* = 9.1, 4.8, 1.8 Hz, 1H), 2.29 – 2.20 (m, 1H), 2.19 – 2.03 (m, 1H), 1.90 – 1.80 (m, 2H), 1.80 – 1.67 (m, 3H), 1.68 – 1.61 (m, 3H), 1.27 – 1.12 (m, 1H), 1.04 – 0.93 (m, 21H), 0.81 (t, *J* = 7.4 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.21 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 203.3, 131.0, 126.5, 83.9, 70.4, 68.8, 60.9, 59.8, 40.1, 39.7, 38.9, 36.2, 26.3, 26.1, 18.6, 18.5, 18.2, 18.2, 12.9, 12.5, 9.4, -2.7, -4.0, -4.0, -4.5. HRMS calc *m/z* $[C_{29}H_{60}O_4Si_2 + Na]^+$:

551.3928, found: 551.3913.



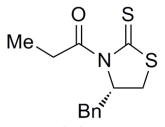
4.43

(*2Z,4S,5S,7R,8R,9R,10S,12E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-4-ethyl-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (4.43). The product was synthesized following the procedure for the synthesis of intermediate **4.32**. Reaction with aldehyde **4.42** (28.2 mg, 0.0533 mmol) resulted in 23.0 mg of product as a colorless oil (72% yield) after purification via silica gel flash chromatography (3% ether in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.11 (dd, *J* = 11.7, 10.0 Hz, 1H), 5.96 (d, *J* = 11.6 Hz, 1H), 5.57 – 5.34 (m, 2H), 4.49 (dd, *J* = 9.9, 4.3 Hz, 1H), 4.10 – 3.93 (m, 2H), 3.93 – 3.82 (m, 2H), 3.51 (s, 3H), 3.37 (dd, *J* = 9.6, 1.7 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.22 – 2.09 (m, 1H), 2.07 – 1.74 (m, 4H), 1.71 – 1.64 (m, 3H), 1.64 – 1.54 (m, 1H), 1.45 – 1.27 (m, 2H), 1.05 (s, 9H), 1.04 (s, 9H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.6 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.27 (s, 3H), 0.25 (s, 3H), 0.24 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 166.0, 151.9, 131.2, 126.4, 121.7, 84.1, 72.8, 69.6, 61.0, 59.7, 46.1, 40.7, 40.1, 39.0, 36.3, 26.4, 26.4, 23.5, 18.7, 18.4, 18.2, 14.3, 13.0, 12.3, 9.6, -2.5, -3.9, -3.9, -4.0. HRMS calc *m/z* $[C_{33}H_{66}O_5Si_2 + Na]^+$: 621.4347, found: 621.4255.



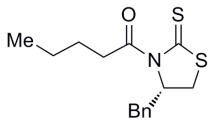
4.22

(*5S,6S*)-5-Ethyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (4.22). The product was synthesized following the procedure for the synthesis of analog **4.20**. Reaction with ester **4.43** (23.0 mg, 0.0384 mmol) resulted in 2.18 mg of product as a colorless oil (18% yield) after purification via silica gel flash chromatography (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 9.8, 6.1 Hz, 1H), 6.04 (dd, *J* = 9.7, 0.9 Hz, 1H), 5.55 – 5.29 (m, 2H), 4.70 (td, *J* = 7.4, 3.5 Hz, 1H), 4.03 (dd, *J* = 7.6, 3.0 Hz, 1H), 3.49 (s, 3H), 3.25 (d, *J* = 3.4 Hz, 1H), 3.09 (t, *J* = 5.7 Hz, 1H), 2.37 (dq, *J* = 9.9, 4.6 Hz, 1H), 2.19 – 2.03 (m, 2H), 1.96 – 1.84 (m, 1H), 1.83 – 1.71 (m, 2H), 1.70 – 1.61 (m, 5H), 1.56 – 1.43 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 150.5, 129.2, 126.8, 120.8, 89.2, 79.1, 68.5, 61.5, 39.3, 37.4, 37.4, 36.1, 35.6, 20.6, 18.0, 14.4, 11.7, 10.9. HRMS calc *m/z* $[C_{19}H_{32}O_4 + Na]^+$: 347.2193, found: 347.2193. 98% pure by HPLC analysis.



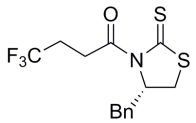
4.45a

(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)propan-1-one (4.45a). The product was synthesized following the procedure for the synthesis of thiazolidinethione **4.39**. Reaction with (*S*)-4-benzylthiazolidine-2-thione (0.20 g, 0.96 mmol) and propionyl chloride (0.09 mL, 1.00 mmol) resulted in 0.190 g of product as a yellow solid (75% yield) after purification via silica gel flash chromatography. The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[133]



4.45b

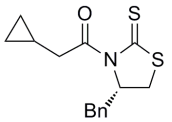
(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)pentan-1-one (4.45b). The product was synthesized following the procedure for the synthesis of thiazolidinethione **4.39**. Reaction with (*S*)-4-benzylthiazolidine-2-thione (0.20 g, 0.96 mmol) and pentanoyl chloride (0.12 mL, 1.0 mmol) resulted in 0.225 g of product as a yellow oil (80% yield) after purification via silica gel flash chromatography (50% DCM in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.37 (ddd, *J* = 10.7, 7.1, 3.9 Hz, 1H), 3.45 – 3.27 (m, 2H), 3.27 – 3.09 (m, 2H), 3.04 (dd, *J* = 13.2, 10.5 Hz, 1H), 2.88 (d, *J* = 11.5 Hz, 1H), 1.68 (ddddd, *J* = 15.9, 14.8, 13.4, 8.4, 6.3 Hz, 2H), 1.39 (h, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 174.2, 136.6, 129.4, 128.9, 127.2, 68.6, 38.2, 36.8, 31.9, 26.8, 22.2, 13.9. $[\alpha]_D$ = +204 (*c* 0.232, $CHCl_3$). HRMS calc *m*/*z* $[C_{15}H_{19}NOS_2 + Na]^+$: 316.0800, found: 316.0770.



4.45c

(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)-4,4,4-trifluorobutan-1-one (4.45c). To a solution of (*S*)-4-benzylthiazolidine-2-thione (0.20 g, 0.96 mmol), 4,4,4-trifluorobutyric acid (0.18 g, 1.2 mmol), and DMAP (15 mg, 0.012 mmol) in DCM (1.3 mL) at 0 °C was added DCC (0.26 g, 1.2 mmol). The reaction was stirred at 0 °C for 10 min before warming to room temperature and stirring an additional 3.5 h. Solid precipitates were removed via filtration through a cotton plug. The filtrate was washed with saturated

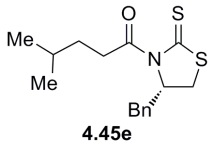
aqueous $NaHCO_3$ and brine before drying with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (10% EtOAc in hexanes) to yield 0.238 g of product as a yellow solid (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.39 (ddd, *J* = 10.8, 7.1, 4.1 Hz, 1H), 3.71 (ddd, *J* = 18.4, 9.6, 5.6 Hz, 1H), 3.50 – 3.31 (m, 2H), 3.21 (dd, *J* = 13.2, 4.1 Hz, 1H), 3.05 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.92 (d, *J* = 11.6 Hz, 1H), 2.68 – 2.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 171.0, 136.2, 129.4, 128.9, 127.3, 126.6 (q, *J* = 276.1 Hz), 68.5, 36.7, 32.1, 32.0 (q, *J* = 3.1 Hz), 29.1 (q, *J* = 29.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.4. $[\alpha]_D$ = +160 (*c* 0.176, $CHCl_3$). HRMS calc *m/z* $[C_{14}H_{14}F_3NOS_2 + Na]^+$: 356.0361, found: 356.0373. mp: 72.9 – 73.6 °C.



4.45d

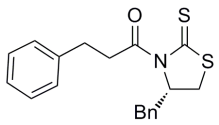
(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)-2-cyclopropylethanone (4.45d). The product was synthesized following the procedure for the synthesis of thiazolidinethione **4.45c**. Reaction with (*S*)-4-benzylthiazolidine-2-thione (0.20 g, 0.96 mmol) and cyclopropylacetic acid (0.124 g, 1.24 mmol) resulted in 0.237 g of product as a yellow solid (85% yield) after purification via silica gel flash chromatography (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.40 (ddd, *J* = 10.8, 7.1, 3.8 Hz, 1H), 3.48 – 3.30 (m, 2H), 3.25 (dd, *J* = 13.2, 3.8 Hz, 1H), 3.16 – 2.99 (m, 2H), 2.89 (d, *J* = 11.6 Hz, 1H), 1.15 (tdd, *J* = 7.9, 6.2, 3.5 Hz, 1H), 0.60 (dqd, *J* = 10.0, 5.6, 3.0 Hz, 2H), 0.20 (dtt, *J* = 16.5, 9.5, 4.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2,

173.9, 136.6, 129.5, 128.9, 127.2, 68.7, 43.8, 36.8, 32.0, 6.6, 4.4, 4.2. $[\alpha]_D$ = +208 (*c* 0.202, $CHCl_3$). HRMS calc *m*/*z* $[C_{15}H_{17}NOS_2 + Na]^+$: 314.0644, found: 314.0671. mp: 88.1 – 88.8 °C.



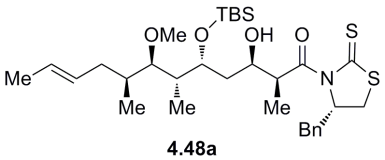
4.45e

(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)-4-methylpentan-1-one (4.45e). The product was synthesized following the procedure for the synthesis of thiazolidinethione **4.45c**. Reaction with (*S*)-4-benzylthiazolidine-2-thione (0.20 g, 0.96 mmol) and 4-methylpentanoic acid (0.144 g, 1.24 mmol) resulted in 0.268 g of product as a yellow solid (91% yield) after purification via silica gel flash chromatography (10% EtOAc in hexanes). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[99]



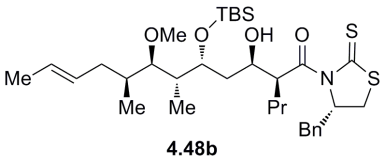
4.45f

(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)-3-phenylpropan-1-one (4.45f). The product was synthesized following the procedure for the synthesis of thiazolidinethione **4.39**. Reaction with (*S*)-4-benzylthiazolidine-2-thione (0.20 g, 0.96 mmol) and 3-phenylpropanoyl chloride (0.15 mL, 1.0 mmol) resulted in 0.296 g of product as a yellow solid (91% yield) after purification via silica gel flash chromatography (40% to 50% DCM in hexanes). The resonances in the ^{1}H NMR and ^{13}C spectrum of the product matched previously reported chemical shifts.[99]



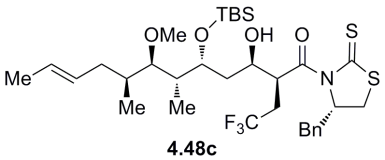
4.48a

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-7-methoxy-2,6,8-trimethyldodec-10-en-1-one (4.48a). The product was synthesized following the procedure for the synthesis of intermediate **4.40**. Reaction with thiazolidinethione **4.45a** (131 mg, 0.493 mmol) and aldehyde **4.25** (49 mg, 0.14 mmol) resulted in 73.9.8 mg of product as a yellow oil (85% yield) after purification via silica gel flash chromatography (7:1 hexanes:EtOAc and subsequently 10% acetones in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 7.12 – 7.00 (m, 3H), 7.01 – 6.90 (m, 2H), 5.57 – 5.34 (m, 2H), 4.99 (ddd, *J* = 10.6, 7.0, 3.7 Hz, 1H), 4.76 (dd, *J* = 6.9, 3.2 Hz, 1H), 4.42 – 4.28 (m, 2H), 3.47 (s, 3H), 3.27 (dd, *J* = 8.8, 1.9 Hz, 1H), 3.13 (bs, 1H), 3.02 (dd, *J* = 13.2, 3.7 Hz, 1H), 2.65 (dd, *J* = 13.2, 10.6 Hz, 1H), 2.42 (dd, *J* = 11.6, 7.1 Hz, 1H), 2.27 (dt, *J* = 12.7, 5.9 Hz, 1H), 2.15 – 2.04 (m, 1H), 2.05 – 1.96 (m, 2H), 1.98 – 1.85 (m, 1H), 1.82 – 1.68 (m, 2H), 1.66 (d, *J* = 4.3 Hz, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.07 – 0.98 (m, 26H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.24 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 201.4, 178.0, 136.9, 131.0, 129.7, 129.0, 128.6, 127.2, 126.6, 84.3, 71.1, 70.1, 69.1, 60.5, 44.6, 41.7, 40.7, 39.0, 36.7, 36.1, 31.6, 26.3, 18.6, 18.3, 13.6, 11.1, 11.1, -3.4, -3.9. HMRS calc *m/z* $[C_{32}H_{53}NO_4S_2Si + Na]^+$: 630.3077, found: 630.3072.



4.48b

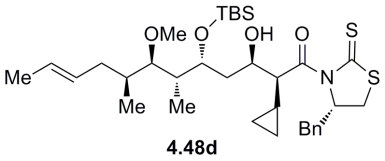
(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-7-methoxy-6,8-dimethyl-2-propyldodec-10-en-1-one (4.48b). The product was synthesized following the procedure for the synthesis of intermediate **4.40**. Reaction with thiazolidinethione **4.45b** (0.123 g, 0.419 mmol) and aldehyde **4.25** (41.5 mg, 0.121 mmol) resulted in 59.4 mg of product as a yellow oil (77% yield) after purification via silica gel flash chromatography (7:1 hexanes:acetone followed by 7:1 hexanes:EtOAc followed by 30% ether in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 7.11 – 7.01 (m, 3H), 7.01 – 6.93 (m, 2H), 5.54 – 5.38 (m, 2H), 5.28 (dt, *J* = 8.9, 4.3 Hz, 1H), 5.12 (ddd, *J* = 10.7, 7.0, 3.7 Hz, 1H), 4.35 (td, *J* = 5.7, 2.6 Hz, 1H), 4.25 (dt, *J* = 8.4, 3.9 Hz, 1H), 3.45 (s, 3H), 3.26 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.12 (dd, *J* = 13.1, 3.7 Hz, 1H), 2.72 (dd, *J* = 13.1, 10.6 Hz, 1H), 2.60 – 2.39 (m, 1H), 2.35 – 2.20 (m, 1H), 2.21 – 2.00 (m, 4H), 1.98 – 1.84 (m, 2H), 1.80 – 1.62 (m, 5H), 1.62 – 1.49 (m, 2H), 1.08 – 0.99 (m, 12H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.24 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.2, 176.5, 137.0, 130.9, 129.7, 129.0, 127.2, 126.6, 84.6, 71.7, 70.9, 69.5, 60.5, 49.6, 41.8, 40.8, 39.0, 36.9, 36.1, 31.4, 29.7, 26.3, 21.2, 18.6, 18.2, 14.7, 13.6, 11.3, -3.4, -3.9. HRMS calc *m/z* $[C_{34}H_{57}NO_4S_2Si + Na]^+$: 658.3390, found: 658.3372.



4.48c

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-7-methoxy-6,8-dimethyl-2-(2,2,2-trifluoroethyl)dodec-10-en-1-one (4.48c). The product was synthesized following the

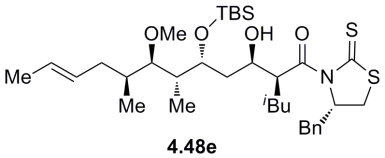
procedure for the synthesis of intermediate **4.40**. Reaction with thiazolidinethione **4.45c** (0.171 g, 0.513 mmol) and aldehyde **4.25** (51 mg, 0.15 mmol) resulted in 70.8 mg of product as a yellow oil (70% yield) after purification via silica gel flash chromatography (15% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 7.11 – 6.98 (m, 3H), 6.99 – 6.90 (m, 2H), 5.88 (dt, *J* = 10.0, 2.7 Hz, 1H), 5.55 – 5.35 (m, 2H), 5.11 (ddd, *J* = 10.5, 7.1, 3.3 Hz, 1H), 4.47 – 4.32 (m, 1H), 4.23 (q, *J* = 4.8 Hz, 1H), 3.41 (s, 3H), 3.36 – 3.16 (m, 2H), 3.07 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.91 (s, 1H), 2.62 (dd, *J* = 13.3, 10.8 Hz, 1H), 2.52 – 2.33 (m, 2H), 2.32 – 2.16 (m, 1H), 2.15 – 2.02 (m, 2H), 1.98 (dd, *J* = 11.6, 2.4 Hz, 1H), 1.92 – 1.80 (m, 2H), 1.76 – 1.63 (m, 4H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.97 (s, 9H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.3, 173.3, 136.9, 130.7, 129.7, 129.0, 127.3, 126.9, 84.7, 71.9, 70.3, 69.7, 60.3, 44.6 (d, *J* = 1.6 Hz), 41.4, 40.5, 39.1, 36.5, 36.1, 30.9 (q, *J* = 29.1 Hz), 30.8, 26.2, 18.5, 18.3, 13.9, 11.8, -3.6, -4.1. Quaternary -CF_3 ^{13}C resonance not observed in spectrum. ^{19}F NMR (376 MHz, C_6D_6) δ -64.0 HRMS calc *m/z* $[C_{33}H_{52}F_3NO_4S_2Si + Na]^+$: 698.2951, found: 698.2948.



4.48d

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-2-cyclopropyl-3-hydroxy-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.48d). The product was synthesized following the procedure for the synthesis of intermediate **4.40**. Reaction with thiazolidinethione **4.45d** (0.153 g, 0.525 mmol) and aldehyde **4.25** (52.1 mg, 0.152 mmol) resulted in 69.2 mg of product as a yellow oil (72% yield) after purification via silica gel flash chromatography (15% EtOAc in hexanes

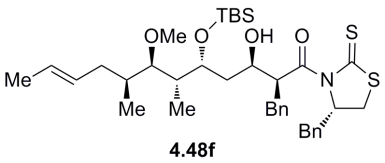
followed by three times with 10% acetone in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 7.13 – 6.99 (m, 3H), 7.01 – 6.94 (m, 2H), 5.57 – 5.38 (m, 2H), 5.10 (ddd, *J* = 10.7, 7.0, 3.6 Hz, 1H), 4.74 (dd, *J* = 9.8, 4.0 Hz, 1H), 4.45 (dt, *J* = 10.5, 3.0 Hz, 1H), 4.38 (tt, *J* = 6.2, 3.2 Hz, 1H), 3.47 (s, 3H), 3.30 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.18 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.05 (bs, 1H), 2.72 (dd, *J* = 13.1, 10.8 Hz, 1H), 2.49 (dd, *J* = 11.6, 7.2 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.24 – 1.92 (m, 5H), 1.77 – 1.69 (m, 1H), 1.66 (d, *J* = 4.3 Hz, 3H), 1.49 – 1.30 (m, 1H), 1.12 – 0.97 (m, 15H), 0.63 (dd, *J* = 9.4, 4.6 Hz, 1H), 0.58 – 0.44 (m, 2H), 0.41 – 0.31 (m, 1H), 0.25 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.3, 176.3, 137.0, 130.9, 129.6, 129.0, 128.6, 127.2, 126.6, 84.2, 72.0, 71.2, 69.7, 60.2, 53.9, 41.6, 40.5, 39.2, 37.0, 36.0, 31.4, 26.3, 18.6, 18.3, 13.9, 11.5, 9.1, 5.6, 2.8, -3.4, -3.9. HRMS calc *m/z* $[C_{34}H_{55}NO_4S_2Si + Na]^+$: 656.3240, found: 656.3242.



4.48e

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-isobutyl-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.48e). The product was synthesized following the procedure for the synthesis of intermediate **4.40**. Reaction with thiazolidinethione **4.45e** (0.141 g, 0.459 mmol) and aldehyde **4.25** (45.5 mg, 0.133 mmol) resulted in 53.0 mg of product as a yellow oil (61% yield) after purification via silica gel flash chromatography (30% ether in hexanes followed by 7:1 hexanes:acetone). ^{1}H NMR (400 MHz, C_6D_6) δ 7.12 – 6.91 (m, 5H), 5.56 – 5.48 (m, 1H), 5.45 (t, *J* = 4.8 Hz, 2H), 5.13 (ddd, *J* = 10.7, 7.0, 3.7 Hz, 1H), 4.36 (td, *J* = 5.8, 2.7 Hz, 1H), 4.23 (tt, *J* = 7.1, 4.1 Hz, 1H), 3.46 (s, 3H), 3.27 (dd, *J* = 8.7, 2.1

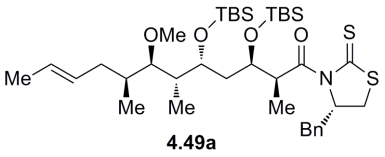
Hz, 1H), 3.15 (dd, *J* = 13.1, 3.6 Hz, 1H), 2.73 (dd, *J* = 13.2, 10.7 Hz, 1H), 2.49 (dd, *J* = 11.2, 7.0 Hz, 1H), 2.43 (d, *J* = 3.8 Hz, 1H), 2.34 – 2.17 (m, 2H), 2.17 – 2.05 (m, 2H), 2.01 (d, *J* = 11.6 Hz, 1H), 1.94 (t, *J* = 5.6 Hz, 2H), 1.89 – 1.79 (m, 1H), 1.73 (ddd, *J* = 13.7, 6.9, 1.8 Hz, 1H), 1.66 (d, *J* = 4.0 Hz, 3H), 1.44 (ddd, *J* = 13.7, 8.0, 3.5 Hz, 1H), 1.10 – 1.00 (m, 18H), 0.97 (d, *J* = 6.9 Hz, 4H), 0.25 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.5, 176.0, 137.0, 130.9, 129.7, 128.9, 128.5, 127.2, 126.6, 84.6, 71.7, 71.3, 69.8, 60.5, 48.0, 41.7, 40.6, 39.1, 36.9, 36.1, 36.0, 31.2, 26.9, 26.3, 23.7, 22.9, 18.6, 18.2, 13.7, 11.3, -3.4, -3.9. HRMS calc *m/z* $[C_{35}H_{59}NO_4S_2Si + Na]^+$: 672.3553, found: 672.3518.



4.48f

(*2S,3R,5R,6R,7R,8S,E*)-2-Benzyl-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.48f). The product was synthesized following the procedure for the synthesis of intermediate **4.40**. Reaction with thiazolidinethione **4.45f** (0.140 g, 0.410 mmol) and aldehyde **4.25** (40.8 mg, 0.119 mmol) resulted in 51.6 mg of product as a yellow oil (63% yield) after purification via silica gel flash chromatography (7:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, C_6D_6) δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.14 – 7.09 (m, 2H), 7.10 – 6.95 (m, 4H), 6.93 – 6.83 (m, 2H), 5.85 (ddd, *J* = 9.3, 5.8, 4.0 Hz, 1H), 5.54 – 5.38 (m, 2H), 5.07 (ddd, *J* = 10.6, 7.1, 3.5 Hz, 1H), 4.43 – 4.28 (m, 2H), 3.52 – 3.39 (m, 1H), 3.43 (s, 3H), 3.24 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.09 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.81 (s, 1H), 2.73 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.49 (dd, *J* = 13.3, 10.6 Hz, 1H), 2.41 (dd, *J* = 11.6, 7.3 Hz, 1H), 2.35

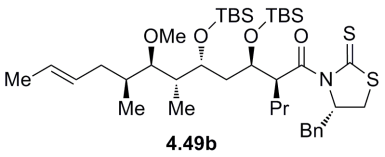
– 2.16 (m, 1H), 2.17 – 2.04 (m, 2H), 2.04 – 1.89 (m, 3H), 1.73 (dd, *J* = 8.2, 6.2 Hz, 1H), 1.66 (d, *J* = 4.2 Hz, 3H), 1.07 – 1.00 (m, 12H), 0.97 (d, *J* = 7.0 Hz, 4H), 0.23 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.1, 175.6, 130.9, 129.8, 129.6, 128.9, 128.7, 128.5, 127.1, 126.6, 126.6, 84.6, 71.9, 70.6, 69.2, 60.4, 50.9, 41.6, 40.5, 39.1, 36.7, 36.1, 33.4, 31.0, 26.3, 18.6, 18.2, 13.7, 11.4, -3.4, -3.9. HRMS calc *m/z* [$C_{38}H_{57}NO_4S_2Si$ + Na]$^+$: 706.3396, found: 706.3363.



4.49a

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,6,8-trimethyldodec-10-en-1-one (4.49a). The product was synthesized following the procedure for the synthesis of intermediate **4.41**. Reaction with alcohol **4.48a** (70.9 mg, 0.117 mmol) resulted in 109 mg of product as a yellow oil (94% yield) after purification via silica gel flash chromatography (100:3 hexanes:EtOAc). ^{1}H NMR (400 MHz, C_6D_6) δ 7.13 – 6.97 (m, 5H), 5.57 – 5.37 (m, 2H), 5.16 (ddd, *J* = 10.6, 6.9, 3.5 Hz, 1H), 5.00 (qd, *J* = 6.8, 4.2 Hz, 1H), 4.36 (dd, *J* = 9.0, 4.6 Hz, 1H), 4.25 (dt, *J* = 7.6, 4.7 Hz, 1H), 3.51 (s, 3H), 3.37 – 3.28 (m, 1H), 3.16 (dd, *J* = 13.1, 3.5 Hz, 1H), 2.82 – 2.65 (m, 2H), 2.36 – 2.05 (m, 5H), 1.95 – 1.81 (m, 1H), 1.75 (q, *J* = 7.1 Hz, 1H), 1.65 (d, *J* = 3.9 Hz, 3H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.09 – 0.99 (m, 21H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.26 (s, 3H), 0.24 (s, 3H), 0.21 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 200.9, 176.6, 137.2, 131.2, 129.7, 129.0, 128.6, 127.2, 126.5, 84.1, 72.1, 69.8, 69.5, 61.2, 45.1, 42.7, 41.4, 39.0, 36.7, 36.2, 31.6, 26.4, 26.2, 18.7, 18.3, 18.3,

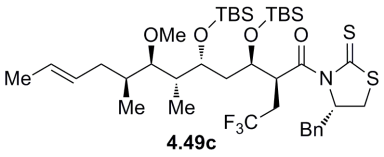
13.3, 10.1, -2.4, -3.8, -4.0, -4.1. HRMS calc *m/z* $[C_{38}H_{67}NO_4S_2Si_2 + Na]^+$: 744.3942, found: 744.3884.



4.49b

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6,8-dimethyl-2-propyldodec-10-en-1-one (4.49b). To a solution of alcohol **4.48b** (59.4 mg, 0.0934 mmol) and 2,6-lutidine (22 µL, 0.19 mmol) in DCM (0.85 mL) at 0 °C was added TBSOTf (32 µL, 0.14 mmol) dropwise. The reaction was removed from the ice bath and stirred at room temperature. The reaction was incomplete by TLC analysis after 30 min and cooled to 0 °C. Additional 2,6-lutidine (16 µL, 0.14 mmol) was added to the reaction followed by the addition TBSOTf (21 µL, 0.093 mmol) dropwise. The reaction was removed from the ice bath and stirred at room temperature. After 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extract three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (100:3 hexanes:EtOAc) to yield 60.7 mg of product as a yellow oil (87% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 7.14 – 6.98 (m, 5H), 5.53 – 5.36 (m, 2H), 5.27 – 5.10 (m, 2H), 4.40 (dd, *J* = 9.4, 4.2 Hz, 1H), 4.21 (dt, *J* = 8.0, 4.4 Hz, 1H), 3.54 (s, 3H), 3.34 (dd, *J* = 9.7, 1.7 Hz, 1H), 3.24 (dd, *J* = 13.1, 3.4 Hz, 1H), 2.88 – 2.69 (m, 2H), 2.40 – 2.22 (m, 3H), 2.23 – 2.05 (m, 3H), 1.94 – 1.81 (m, 2H), 1.81 – 1.56 (m, 6H), 1.09 –

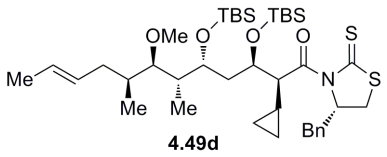
0.98 (m, 25H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.31 (s, 3H), 0.29 (s, 3H), 0.21 (s, 3H), 0.21 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 201.2, 176.0, 137.2, 131.1, 129.7, 129.0, 127.2, 126.4, 84.0, 71.8, 69.9, 69.8, 61.1, 50.1, 42.7, 41.3, 38.9, 36.7, 36.2, 31.5, 30.9, 26.3, 26.2, 21.3, 18.7, 18.3, 18.2, 14.8, 13.2, 10.1, -2.5, -3.8, -4.1, -4.1. HRMS calc *m/z* $[C_{40}H_{71}NO_4S_2Si_2 + Na]^+$: 772.4261, found: 772.4137.



4.49c

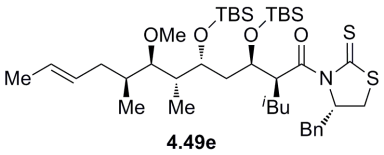
(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6,8-dimethyl-2-(2,2,2-trifluoroethyl)dodec-10-en-1-one (4.49c). The product was synthesized following the procedure for the synthesis of intermediate **4.49b**. Reaction with alcohol **4.48c** (70.2 mg, 0.104 mmol) resulted in 66.5 mg of product as a yellow oil (81% yield) after purification via silica gel flash chromatography (100:3 hexanes:EtOAc followed by 100:3 hexanes:acetone, and 4% ether in hexanes twice). ^{1}H NMR (400 MHz, C_6D_6) δ 7.11 – 6.92 (m, 5H), 5.88 (d, *J* = 9.9 Hz, 1H), 5.56 – 5.35 (m, 2H), 5.10 (ddd, *J* = 10.3, 6.7, 3.2 Hz, 1H), 4.38 (dd, *J* = 9.0, 5.1 Hz, 1H), 4.16 (s, 1H), 3.58 (d, *J* = 0.9 Hz, 3H), 3.55 – 3.37 (m, 1H), 3.30 (d, *J* = 9.5 Hz, 1H), 3.18 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.77 – 2.52 (m, 3H), 2.36 – 2.22 (m, 1H), 2.21 – 2.07 (m, 2H), 2.07 – 1.94 (m, 2H), 1.88 – 1.70 (m, 2H), 1.65 (d, *J* = 3.9 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.02 (s, 8H), 0.98 (s, 7H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.27 (s, 6H), 0.11 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 201.0, 173.1, 137.1, 131.0, 129.7, 129.1, 127.3, 126.6, 83.8, 70.9, 70.2, 68.7, 61.2, 45.1, 43.5, 41.2, 38.9, 36.3, 36.2, 31.3, 30.7 (q, *J* = 29.1 Hz), 26.3, 26.1, 18.6, 18.3, 18.3, 13.4, 10.2, -2.8, -3.9, -3.9, -4.7. Quaternary -

CF_3 ^{13}C resonance not observed in spectrum. ^{19}F NMR (376 MHz, C_6D_6) δ -63.6. HRMS calc *m/z* $[C_{39}H_{66}F_3NO_4S_2Si_2 + Na]^+$: 812.3822, found: 812.3812.



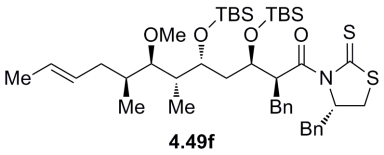
4.49d

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-cyclopropyl-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.49d). The product was synthesized following the procedure for the synthesis of intermediate **4.49b**. Reaction with alcohol **4.48d** (67.8 mg, 0.107 mmol) resulted in 75.4 mg of product as a yellow oil (93% yield) after purification via silica gel flash chromatography (100:3 hexanes:EtOAc followed by 4% ether in hexanes). ^1H NMR (400 MHz, C_6D_6) δ 7.14 – 6.97 (m, 5H), 5.60 – 5.37 (m, 2H), 5.15 (ddd, *J* = 10.6, 6.9, 3.3 Hz, 1H), 4.86 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.66 (dd, *J* = 9.4, 4.7 Hz, 1H), 4.28 (dt, *J* = 8.3, 4.4 Hz, 1H), 3.49 (s, 3H), 3.38 (dd, *J* = 9.8, 1.5 Hz, 1H), 3.28 (dd, *J* = 13.0, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.1, 10.8 Hz, 1H), 2.67 (dd, *J* = 11.5, 7.0 Hz, 1H), 2.43 (ddd, *J* = 13.3, 7.9, 4.6 Hz, 1H), 2.34 – 2.21 (m, 1H), 2.20 – 2.06 (m, 3H), 1.96 (p, *J* = 7.1 Hz, 1H), 1.77 (q, *J* = 7.1 Hz, 1H), 1.72 – 1.62 (m, 3H), 1.62 – 1.48 (m, 1H), 1.11 – 1.00 (m, 22H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.76 (dp, *J* = 9.0, 4.7 Hz, 1H), 0.56 (ddp, *J* = 24.2, 9.6, 5.0 Hz, 2H), 0.35 (s, 3H), 0.35 (s, 3H), 0.21 (s, 3H), 0.20 (s, 3H) ^{13}C NMR (100 MHz, C_6D_6) δ 201.7, 175.9, 137.4, 131.2, 129.8, 129.0, 128.6, 127.2, 126.5, 84.0, 73.0, 70.2, 69.6, 61.2, 54.1, 43.0, 41.0, 38.9, 36.8, 36.2, 31.5, 26.4, 26.3, 18.8, 18.3, 18.3, 13.3, 11.1, 10.1, 5.6, 3.9, -2.0, -3.7, -4.1, -4.3. HRMS calc *m/z* $[C_{40}H_{69}NO_4S_2Si_2 + Na]^+$: 770.4068, found: 770.4068.



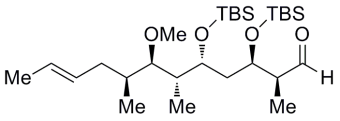
4.49e

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-isobutyl-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.49e). The product was synthesized following the procedure for the synthesis of intermediate **4.49b**. Reaction with alcohol **4.48e** (51.6 mg, 0.0794 mmol) resulted in 49.2 mg of product as a yellow oil (81% yield) after purification via silica gel flash chromatography (100:3 hexanes:ether). ^{1}H NMR (400 MHz, C_6D_6) δ 7.11 – 6.97 (m, 5H), 5.60 – 5.39 (m, 2H), 5.34 (dt, *J* = 9.6, 4.0 Hz, 1H), 5.16 (ddd, *J* = 10.5, 6.8, 3.5 Hz, 1H), 4.41 (dd, *J* = 9.7, 4.4 Hz, 1H), 4.20 (ddd, *J* = 7.8, 4.8, 3.1 Hz, 1H), 3.55 (s, 3H), 3.36 (dd, *J* = 9.6, 1.6 Hz, 1H), 3.27 (dd, *J* = 13.1, 3.4 Hz, 1H), 2.88 – 2.69 (m, 2H), 2.41 (ddd, *J* = 13.6, 9.6, 6.3 Hz, 1H), 2.34 – 2.07 (m, 5H), 2.03 – 1.94 (m, 1H), 1.94 – 1.86 (m, 1H), 1.86 – 1.72 (m, 1H), 1.74 – 1.59 (m, 4H), 1.13 (d, *J* = 5.3 Hz, 4H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 1.02 (s, 9H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.31 (s, 3H), 0.29 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 201.0, 175.7, 137.3, 131.2, 129.8, 129.1, 127.2, 126.5, 84.0, 71.8, 70.1, 69.7, 61.1, 48.6, 42.4, 41.2, 39.0, 36.7, 36.4, 36.3, 31.5, 26.8, 26.4, 26.2, 23.7, 23.3, 18.7, 18.3, 18.3, 13.5, 10.2, -2.4, -3.6, -3.8, -4.2. HRMS calc *m/z* $[C_{41}H_{73}NO_4S_2Si_2 + Na]^+$: 786.4417, found: 786.4306.



4.49f

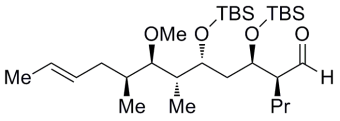
(*2S,3R,5R,6R,7R,8S,E*)-2-Benzyl-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.49f). The product was synthesized following the procedure for the synthesis of intermediate **4.41**. Reaction with alcohol **4.48f** (51.6 mg, 0.0754 mmol) resulted in 47.1 mg of product as a yellow oil (78% yield) after purification via silica gel flash chromatography (100:3 hexanes:EtOAc). ^{1}H NMR (400 MHz, C_6D_6) δ 7.66 – 7.58 (m, 2H), 7.24 – 7.18 (m, 2H), 7.10 – 6.99 (m, 4H), 6.98 – 6.91 (m, 2H), 5.83 (ddd, *J* = 9.1, 6.1, 3.3 Hz, 1H), 5.60 – 5.35 (m, 2H), 5.14 (ddd, *J* = 10.5, 6.9, 3.4 Hz, 1H), 4.49 (dd, *J* = 9.7, 4.4 Hz, 1H), 4.29 (dt, *J* = 7.9, 4.4 Hz, 1H), 3.63 (dd, *J* = 13.9, 8.9 Hz, 1H), 3.56 (s, 3H), 3.37 (dd, *J* = 9.6, 1.6 Hz, 1H), 3.28 (dd, *J* = 14.0, 6.1 Hz, 1H), 2.90 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.69 (dd, *J* = 11.5, 7.0 Hz, 1H), 2.58 (dd, *J* = 13.3, 10.7 Hz, 1H), 2.36 – 2.22 (m, 2H), 2.22 – 2.06 (m, 3H), 1.92 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.78 (q, *J* = 7.1 Hz, 1H), 1.70 – 1.60 (m, 3H), 1.10 – 1.04 (m, 13H), 1.03 (s, 10H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.26 (s, 6H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 201.1, 175.0, 139.8, 137.2, 131.2, 130.1, 129.7, 129.0, 128.7, 128.6, 127.2, 126.7, 126.5, 84.1, 71.3, 69.7, 69.6, 61.2, 51.5, 43.0, 41.2, 39.0, 36.5, 36.3, 33.6, 31.2, 26.4, 26.3, 18.7, 18.4, 18.3, 13.5, 10.1, -2.4, -3.8, -3.9, -4.1. HRMS calc *m/z* $[C_{44}H_{71}NO_4S_2Si_2 + Na]^+$: 820.4261, found: 820.4097.



4.46a

(*2S,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,6,8-trimethyldodec-10-enal (4.46a). To a solution of amide **4.49a** (77.9 mg, 0.108 mmol) in DCM (2.6 mL) at -78 °C was added DIBAL-H (1 M in hexanes, 0.22 mL, 0.22 mmol)

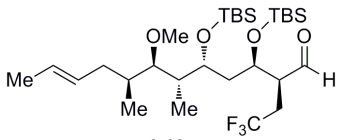
dropwise. The reaction was determined to be complete after the reaction turned from yellow to clear upon addition of DIBAL-H. The reaction was quenched with saturated aqueous Rochelle salt and diluted with DCM and warmed to room temperature. The slurry was stirred at room temperature for 1.5 h. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (4% EtOAc in hexanes) to yield 50.0 mg of product as a colorless oil (90% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 9.53 (s, 1H), 5.56 – 5.33 (m, 2H), 4.34 (ddd, *J* = 8.4, 5.6, 2.0 Hz, 1H), 4.15 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.39 (s, 2H), 3.27 (dd, *J* = 9.9, 1.6 Hz, 1H), 2.39 (qd, *J* = 6.9, 2.2 Hz, 1H), 2.32 – 2.16 (m, 1H), 2.16 – 2.02 (m, 1H), 2.03 – 1.85 (m, 2H), 1.79 – 1.60 (m, 5H), 1.20 (d, *J* = 7.0 Hz, 2H), 0.99 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 8H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.8, 130.9, 126.6, 83.8, 69.1, 68.9, 61.1, 50.1, 40.9, 40.7, 38.8, 36.0, 26.2, 25.9, 18.5, 18.2, 18.2, 13.0, 9.5, 6.8, -2.8, -4.0, -4.2, -4.6. HRMS calc *m/z* $[C_{28}H_{58}O_4Si_2 + Na]^+$: 537.3771, found: 537.3771.



4.46b

(*2S,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6,8-dimethyl-2-propyldodec-10-enal (4.46b) The product was synthesized following the procedure for the synthesis of intermediate **4.46a**. Reaction with amide **4.49b** (59.2 mg, 0.0789

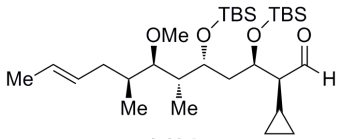
mmol) resulted in 31.4 mg of product as a colorless oil (73% yield) after purification via silica gel flash chromatography (4% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 9.72 (d, *J* = 1.3 Hz, 1H), 5.54 – 5.32 (m, 2H), 4.31 (td, *J* = 8.2, 2.5 Hz, 1H), 4.25 – 4.14 (m, 2H), 3.41 (s, 3H), 3.27 (dd, *J* = 9.7, 1.7 Hz, 1H), 2.41 (d, *J* = 9.8 Hz, 1H), 2.32 – 2.17 (m, 1H), 2.18 – 2.05 (m, 1H), 2.06 – 1.91 (m, 3H), 1.81 – 1.68 (m, 2H), 1.68 – 1.60 (m, 3H), 1.63 – 1.44 (m, 2H), 1.40 – 1.23 (m, 1H), 1.01 – 0.92 (m, 23H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.18 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 203.4, 130.9, 126.5, 83.9, 69.9, 69.3, 61.0, 55.7, 41.1, 40.6, 38.8, 36.1, 26.2, 26.0, 25.5, 21.7, 18.5, 18.2, 18.2, 14.4, 12.9, 9.5, -2.8, -4.1, -4.2, -4.5. HRMS calc *m*/*z* [$C_{30}H_{62}O_4Si_2$ + Na]$^{+}$: 565.4084, found: 565.4067.



4.46c

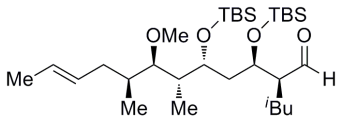
(*2S,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6,8-dimethyl-2-(2,2,2-trifluoroethyl)dodec-10-enal (4.46c). The product was synthesized following the procedure for the synthesis of intermediate **4.42**. Reaction with amide **4.49c** (63.2 mg, 0.0800 mmol) resulted in 24.6 mg of product as a colorless oil (53% yield) after purification via silica gel flash chromatography (100:1 DCM:ether followed by 40% DCM in hexanes to 1% ether in DCM). ^{1}H NMR (400 MHz, C_6D_6) δ 9.41 (s, 1H), 5.55 – 5.30 (m, 2H), 4.33 (dd, *J* = 9.4, 5.1 Hz, 1H), 4.21 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.39 (s, 3H), 3.25 (d, *J* = 9.2 Hz, 1H), 3.08 – 2.89 (m, 1H), 2.85 (d, *J* = 8.5 Hz, 1H), 2.44 – 2.29 (m, 1H), 2.28 – 2.16 (m, 1H), 2.16 – 2.03 (m, 1H), 1.97 (ddd, *J* = 15.1, 10.3, 5.3 Hz, 1H), 1.86 (ddd, *J* = 14.0, 9.5, 5.0 Hz, 1H), 1.77 – 1.58 (m, 5H), 1.01 – 0.93 (m, 12H), 0.87 (d,

J = 6.9 Hz, 3H), 0.84 (s, 9H), 0.13 (s, 6H), 0.03 (s, 3H), -0.05 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 198.9, 130.9, 126.7, 83.7, 68.5, 68.1, 61.1, 49.8 (d, J = 1.8 Hz), 40.8, 40.4, 38.8, 36.1, 26.9 (q, J = 29.3 Hz), 26.1, 25.8, 18.5, 18.3, 18.1, 12.9, 9.4, -3.1, -4.2, -4.3, -4.8. Quaternary -CF_3 ^{13}C resonance not observed in spectrum. ^{19}F NMR (376 MHz, C_6D_6) δ -64.3. HRMS calc m/z $[C_{29}H_{57}F_3O_4Si_2 + Na]^+$: 605.3640, found: 605.3620.



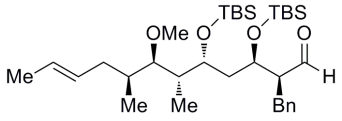
4.46d

(*2S,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-cyclopropyl-7-methoxy-6,8-dimethyldodec-10-enal (4.46d). The product was synthesized following the procedure for the synthesis of intermediate **4.46a**. Reaction with amide **4.49d** (75.4 mg, 0.101 mmol) resulted in 49.2 mg of product as a colorless oil (90% yield) after purification via silica gel flash chromatography (4% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 9.82 (d, J = 1.5 Hz, 1H), 5.56 – 5.32 (m, 2H), 4.42 (ddd, J = 8.4, 5.6, 2.3 Hz, 1H), 4.25 (ddd, J = 9.4, 5.4, 1.2 Hz, 1H), 3.39 (s, 3H), 3.28 (dd, J = 9.7, 1.6 Hz, 1H), 2.34 – 2.15 (m, 2H), 2.13 – 2.03 (m, 1H), 1.98 (ddd, J = 13.4, 9.4, 5.7 Hz, 1H), 1.76 – 1.66 (m, 2H), 1.66 – 1.62 (m, 3H), 1.57 (dt, J = 10.0, 1.9 Hz, 1H), 1.27 – 1.13 (m, 1H), 1.01 (s, 9H), 0.98 – 0.93 (m, 12H), 0.90 (d, J = 6.9 Hz, 3H), 0.61 – 0.43 (m, 2H), 0.27 (dq, J = 9.3, 4.9 Hz, 1H), 0.21 (s, 3H), 0.18 (s, 6H), 0.11 (s, 3H), 0.01 (dq, J = 9.9, 5.1, 4.7 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ 203.9, 131.0, 126.5, 83.8, 70.5, 69.5, 60.9, 60.4, 41.3, 40.5, 38.9, 36.0, 26.3, 26.1, 18.6, 18.3, 18.2, 13.0, 9.5, 5.7, 5.2, 2.6, -2.4, -3.9, -4.0, -4.5. HRMS calc m/z $[C_{30}H_{60}O_4Si_2 + Na]^+$: 563.3922, found: 563.3929.



4.46e

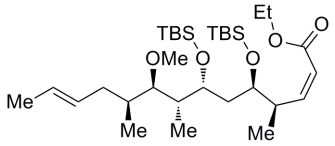
(*2S,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-isobutyl-7-methoxy-6,8-dimethyldodec-10-enal (4.46e). The product was synthesized following the procedure for the synthesis of intermediate **4.42**. Reaction with amide **4.49e** (49.2 mg, 0.0644 mmol) resulted in 29.2 mg of product as a colorless oil (81% yield) after purification via silica gel flash chromatography (4% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 9.76 (d, *J* = 1.6 Hz, 1H), 5.51 – 5.37 (m, 2H), 4.32 (ddd, *J* = 8.6, 6.0, 2.5 Hz, 1H), 4.22 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.41 (s, 3H), 3.29 (dd, *J* = 9.7, 1.7 Hz, 1H), 2.52 (dd, *J* = 10.2, 2.2 Hz, 1H), 2.32 – 2.19 (m, 1H), 2.17 – 1.90 (m, 4H), 1.80 – 1.67 (m, 3H), 1.65 (d, *J* = 4.0 Hz, 3H), 1.40 (ddd, *J* = 14.0, 9.1, 3.0 Hz, 1H), 1.02 – 0.93 (m, 27H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.13 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 203.9, 131.0, 126.5, 83.7, 70.2, 69.1, 60.9, 53.7, 40.8, 40.3, 38.8, 36.1, 32.2, 26.6, 26.2, 26.0, 23.8, 22.1, 18.5, 18.2, 12.9, 9.4, -2.7, -4.1, -4.5. HRMS calc *m*/*z* $[C_{31}H_{64}O_4Si_2 + Na]^+$: 579.4235, found: 579.4234.



4.46f

(*2S,3R,5R,6R,7R,8S,E*)-2-Benzyl-3,5-bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6,8-dimethyldodec-10-enal (4.46f). The product was synthesized following the procedure for the synthesis of intermediate **4.46a**. Reaction with **4.49f** (47.1 mg, 0.0590 mmol) resulted in 28.2 mg of product as a colorless oil (81% yield) after purification via silica

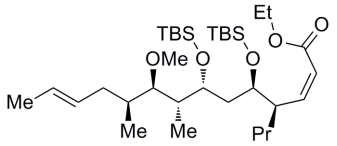
gel flash chromatography (4% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 9.69 (d, *J* = 1.0 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.20 – 7.12 (m, 2H), 7.05 (td, *J* = 7.1, 1.3 Hz, 1H), 5.55 – 5.33 (m, 2H), 4.40 (ddd, *J* = 8.4, 6.0, 2.2 Hz, 1H), 4.28 (dd, *J* = 9.5, 5.4 Hz, 1H), 3.42 (s, 3H), 3.36 (dd, *J* = 14.5, 9.4 Hz, 1H), 3.29 (dd, *J* = 9.7, 1.6 Hz, 1H), 2.98 (dd, *J* = 14.5, 4.2 Hz, 1H), 2.91 – 2.80 (m, 1H), 2.31 – 2.16 (m, 1H), 2.17 – 1.96 (m, 3H), 1.81 – 1.68 (m, 2H), 1.65 (d, *J* = 4.3 Hz, 3H), 1.02 – 0.93 (m, 22H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.5, 140.5, 130.9, 129.4, 128.9, 126.5, 83.8, 69.4, 69.2, 61.0, 57.5, 41.0, 40.4, 38.8, 36.0, 29.3, 26.2, 26.0, 18.5, 18.2, 13.0, 9.5, -2.7, -4.1, -4.1, -4.6. HRMS calc *m*/*z* $[C_{34}H_{62}O_4Si_2 + Na]^+$: 613.4079, found: 613.4087.



4.47a

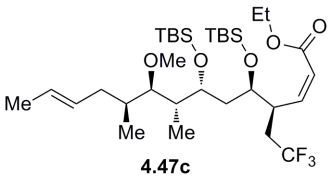
(*2Z,4R,5R,7R,8R,9R,10S,12E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-9-methoxy-4,8,10-trimethyltetradeca-2,12-dienoate (4.47a). The product was synthesized following the procedure for the synthesis of intermediate **4.32**. Reaction with aldehyde **4.46a** (49.2 mg, 0.0955 mmol) resulted in 39.6 mg of product as a colorless oil (71% yield) after purification via silica gel flash chromatography (4% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.22 (dd, *J* = 11.6, 9.5 Hz, 1H), 5.84 (dd, *J* = 11.5, 0.9 Hz, 1H), 5.53 – 5.37 (m, 2H), 4.38 (ddd, *J* = 9.5, 4.8, 1.2 Hz, 1H), 4.10 – 3.90 (m, 4H), 3.54 (d, *J* = 1.5 Hz, 3H), 3.36 (dd, *J* = 9.6, 1.7 Hz, 1H), 2.42 – 2.27 (m, 1H), 2.23 – 2.11 (m, 1H), 2.11 – 1.91 (m, 3H), 1.81 (qd, *J* = 7.2, 1.7 Hz, 1H), 1.73 – 1.56 (m, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 9H), 1.01 – 0.94 (m, 16H), 0.24 (s, 3H), 0.23

(s, 3H), 0.15 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 165.7, 153.8, 131.3, 126.3, 119.1, 84.1, 72.8, 69.5, 61.0, 59.7, 41.9, 40.7, 39.0, 37.1, 36.3, 26.3, 26.1, 18.6, 18.3, 18.2, 14.3, 13.7, 13.2, 9.8, -2.7, -3.9, -4.0, -4.3. HRMS calc *m/z* $[C_{32}H_{64}O_5Si_2 + Na]^+$: 607.4184, found: 607.4182.



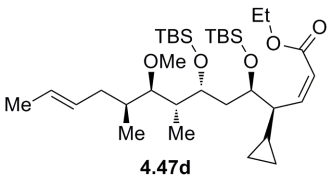
4.47b

(*2Z,4R,5R,7R,8R,9R,10S,12E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-9-methoxy-8,10-dimethyl-4-propyltetradeca-2,12-dienoate (4.47b). The product was synthesized following the procedure for the synthesis of intermediate **4.32**. Reaction with aldehyde **4.46b** (31.4 mg, 0.0578 mmol) resulted in 29.8 mg of product as a colorless oil (84% yield) after purification via silica gel flash chromatography (3% ether in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.17 (dd, *J* = 11.7, 10.0 Hz, 1H), 5.94 (d, *J* = 11.7 Hz, 1H), 5.56 – 5.41 (m, 2H), 4.40 (dd, *J* = 9.8, 4.7 Hz, 1H), 4.11 – 3.88 (m, 4H), 3.54 (s, 3H), 3.39 (dd, *J* = 9.6, 1.7 Hz, 1H), 2.41 – 2.29 (m, 1H), 2.26 – 2.09 (m, 2H), 2.09 – 1.95 (m, 2H), 1.92 – 1.75 (m, 2H), 1.73 – 1.65 (m, 3H), 1.65 – 1.55 (m, 1H), 1.45 (tq, *J* = 13.5, 7.4 Hz, 2H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.07 – 0.94 (m, 27H), 0.26 (s, 3H), 0.25 (s, 3H), 0.17 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 165.8, 153.5, 131.3, 126.3, 120.6, 84.1, 73.1, 69.5, 61.0, 59.7, 42.1, 41.9, 40.5, 39.0, 36.3, 30.9, 26.3, 26.2, 20.9, 18.6, 18.3, 18.2, 14.5, 14.2, 13.2, 9.8, -2.6, -3.9, -4.0, -4.3. HRMS calc *m/z* $[C_{34}H_{68}O_5Si_2 + Na]^+$: 635.4497, found: 635.4536.



4.47c

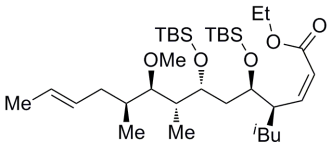
(*2Z,4R,5R,7R,8R,9R,10S,12E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-9-methoxy-8,10-dimethyl-4-(2,2,2-trifluoroethyl)tetradeca-2,12-dienoate (4.47c). The product was synthesized following the procedure for the synthesis of intermediate **4.32**. Reaction with aldehyde **4.46c** (24.6 mg, 0.0422 mmol) resulted in 26.3 mg of product as a colorless oil (95% yield) after purification via silica gel flash chromatography (4% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.17 – 6.03 (m, 1H), 5.86 (dd, *J* = 11.5, 1.0 Hz, 1H), 5.53 – 5.41 (m, 2H), 4.43 – 4.35 (m, 1H), 4.31 (t, *J* = 10.2 Hz, 1H), 4.05 – 3.88 (m, 3H), 3.53 (s, 3H), 3.35 (dd, *J* = 9.6, 1.7 Hz, 1H), 2.75 – 2.54 (m, 1H), 2.41 – 2.24 (m, 2H), 2.24 – 2.11 (m, 1H), 2.08 – 1.88 (m, 3H), 1.80 (qd, *J* = 7.1, 1.7 Hz, 1H), 1.70 – 1.62 (m, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.01 (s, 9H), 0.98 – 0.87 (m, 15H), 0.23 (d, *J* = 0.7 Hz, 6H), 0.08 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 165.4, 150.7, 131.3, 126.4, 121.0, 84.0, 73.0, 68.8, 61.1, 60.0, 42.5, 40.5, 39.0, 37.1 (d, *J* = 2.6 Hz), 36.4, 33.8 (q, *J* = 27.6 Hz), 26.3, 26.1, 18.6, 18.3, 18.3, 14.1, 13.3, 9.7, -2.9, -4.0, -4.1, -4.5. Quaternary -CF_3 ^{13}C resonance not observed in spectrum. ^{19}F NMR (376 MHz, C_6D_6) δ -63.0. HRMS calc *m/z* $[C_{33}H_{63}F_3O_5Si_2 + Na]^+$: 675.4064, found: 675.4087.



4.47d

(*2Z,4R,5R,7R,8R,9R,10S,12E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-4-cyclopropyl-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (4.47d). The product

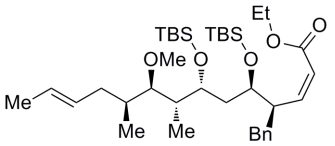
was synthesized following the procedure for the synthesis of **4.32**. Reaction with aldehyde **4.46d** (48.2 mg, 0.0891 mmol) resulted in 48.9 mg of product as a colorless oil (90% yield) after purification via silica gel flash chromatography (100:4 hexanes:EtOAc). ^{1}H NMR (400 MHz, C_6D_6) δ 6.38 (dd, *J* = 11.6, 10.2 Hz, 1H), 5.89 (dd, *J* = 11.7, 0.9 Hz, 1H), 5.54 – 5.38 (m, 2H), 4.50 (ddd, *J* = 9.4, 5.1, 1.3 Hz, 1H), 4.15 (ddd, *J* = 8.4, 5.5, 2.8 Hz, 1H), 4.09 – 3.87 (m, 2H), 3.51 (d, *J* = 0.9 Hz, 3H), 3.40 (dd, *J* = 9.8, 1.5 Hz, 1H), 3.29 (td, *J* = 9.8, 2.7 Hz, 1H), 2.46 – 2.27 (m, 2H), 2.24 – 2.11 (m, 1H), 2.09 – 1.94 (m, 2H), 1.82 (qd, *J* = 7.1, 1.5 Hz, 1H), 1.71 – 1.61 (m, 3H), 1.17 – 1.07 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.01 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.70 – 0.55 (m, 2H), 0.44 – 0.32 (m, 2H), 0.27 (s, 3H), 0.24 (s, 3H), 0.20 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 165.9, 152.2, 131.4, 126.4, 119.2, 84.0, 73.3, 69.9, 61.0, 59.8, 46.9, 41.9, 40.6, 39.1, 36.3, 26.4, 26.2, 18.8, 18.4, 18.3, 14.3, 13.3, 10.8, 9.8, 6.6, 2.5, -2.2, -3.8, -3.9, -4.2 HRMS calc *m/z* $[C_{34}H_{66}O_5Si_2 + Na]^+$: 633.4341, found: 633.4298.



4.47e

(*2Z,4R,5R,7R,8R,9R,10S,12E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-4-isobutyl-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (4.47e). The product was synthesized following the procedure for the synthesis of intermediate **4.32**. Reaction with aldehyde **4.46e** (29.2 mg, 0.0524 mmol) resulted in 23.0 mg of product as a colorless oil (70% yield) after purification via silica gel flash chromatography (3% ether in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.17 (dd, *J* = 11.7, 9.9 Hz, 1H), 5.94 (d, *J* = 11.9 Hz, 1H),

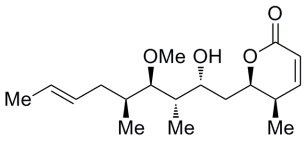
5.57 – 5.40 (m, 2H), 4.41 (dd, *J* = 10.5, 4.5 Hz, 1H), 4.07 (ddd, *J* = 8.8, 5.2, 3.0 Hz, 1H), 4.04 – 3.91 (m, 3H), 3.54 (s, 3H), 3.42 (dd, *J* = 9.7, 1.7 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.27 – 2.09 (m, 3H), 2.03 (ddd, *J* = 13.5, 10.3, 5.2 Hz, 1H), 1.85 (dq, *J* = 6.9, 1.2 Hz, 1H), 1.75 – 1.51 (m, 6H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 5.7 Hz, 3H), 1.06 – 0.95 (m, 27H), 0.27 (s, 3H), 0.25 (s, 3H), 0.16 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 165.8, 154.3, 131.4, 126.3, 120.4, 84.0, 73.3, 69.3, 61.1, 59.8, 41.8, 40.2, 40.1, 39.1, 37.8, 36.4, 26.4, 26.3, 26.2, 24.8, 21.9, 18.7, 18.4, 18.3, 14.3, 13.3, 9.7, -2.4, -3.9, -3.9, -4.3. HRMS calc *m/z* $[C_{35}H_{70}O_5Si_2 + Na]^+$: 649.4654, found: 649.4662.



4.47f

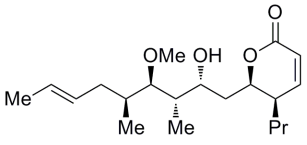
(*2Z,4R,5R,7R,8R,9R,10S,12E*)-Ethyl 4-Benzyl-5,7-bis((*tert*-butyldimethylsilyl)oxy)-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (4.47f). The product was synthesized following the procedure for the synthesis of intermediate **4.32**. Reaction with aldehyde **4.46f** (28.2 mg, 0.0477 mmol) resulted in 27.4 mg of product as a colorless oil (87% yield) after purification via silica gel flash chromatography (4% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 7.43 – 7.30 (m, 2H), 7.23 – 7.12 (m, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.21 (dd, *J* = 11.6, 9.7 Hz, 1H), 5.76 (d, *J* = 11.6 Hz, 1H), 5.49 (q, *J* = 2.9, 1.6 Hz, 2H), 4.55 (dd, *J* = 10.1, 4.8 Hz, 1H), 4.33 (td, *J* = 10.1, 8.2, 4.8 Hz, 1H), 4.16 (ddd, *J* = 8.6, 5.3, 3.0 Hz, 1H), 3.98 – 3.77 (m, 2H), 3.58 (s, 3H), 3.43 (dd, *J* = 9.6, 1.7 Hz, 1H), 3.30 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.89 (dd, *J* = 13.8, 10.5 Hz, 1H), 2.45 – 2.31 (m, 1H), 2.29 – 2.13 (m, 3H), 2.09 (ddd, *J* = 13.6, 10.1, 5.3 Hz, 1H), 1.85 (q, *J* = 7.0 Hz, 1H), 1.73 – 1.61 (m, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.10 – 0.97 (m, 21H), 0.88 (t, *J* = 7.1 Hz, 4H),

0.24 (s, 3H), 0.21 (s, 4H), 0.17 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 165.6, 152.8, 140.4, 131.3, 129.5, 128.6, 126.3, 126.3, 120.7, 84.2, 72.7, 69.4, 61.1, 59.6, 43.8, 42.1, 40.3, 39.1, 36.4, 35.2, 26.3, 26.2, 18.6, 18.4, 18.2, 14.1, 13.3, 9.8, -2.5, -3.9, -4.0, -4.3. HRMS calc *m/z* $[C_{38}H_{68}O_5Si_2 + Na]^+$: 683.4497, found: 683.4513.



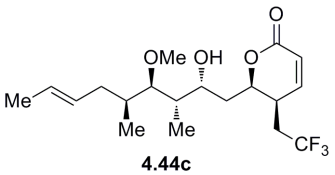
4.44a

(*5R,6R*)-6-((*2R,3S,4R,5S,E*)-2-Hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5-methyl-5,6-dihydro-2*H*-pyran-2-one (4.44a). The product was synthesized following the procedure for the synthesis of analog **4.20**. Reaction with ester **4.47a** (35.9 mg, 0.0614 mmol) resulted in 14.7 mg of product as a white solid (77% yield) after purification via silica gel flash chromatography (25% acetone in hexanes followed by 1:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, C_6D_6) δ 6.05 (dd, *J* = 9.6, 6.1 Hz, 1H), 5.73 (dd, *J* = 9.7, 0.8 Hz, 1H), 5.61 – 5.23 (m, 2H), 4.59 (ddd, *J* = 9.8, 5.4, 3.4 Hz, 1H), 4.38 (ddd, *J* = 6.7, 4.6, 2.3 Hz, 1H), 3.17 (d, *J* = 2.6 Hz, 1H), 3.12 (s, 3H), 2.77 (dd, *J* = 6.4, 4.4 Hz, 1H), 2.18 – 1.94 (m, 1H), 1.89 – 1.75 (m, 2H), 1.75 – 1.65 (m, 2H), 1.62 (dt, *J* = 6.2, 1.3 Hz, 3H), 1.59 – 1.52 (m, 2H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.64 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 163.5, 150.8, 129.5, 126.9, 120.3, 91.0, 77.3, 67.2, 61.4, 39.6, 37.8, 37.5, 36.5, 32.8, 18.1, 15.5, 11.8, 11.4. HRMS calc *m/z* $[C_{18}H_{30}O_4 + Na]^+$: 333.2036, found: 333.2023. 97% pure by HPLC analysis.



4.44b

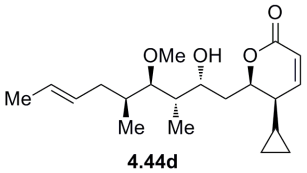
(*5R,6R*)-6-((*2R,3S,4R,5S,E*)-2-Hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5-propyl-5,6-dihydro-2*H*-pyran-2-one (4.44b). The product was synthesized following the procedure for the synthesis of analog **4.20**. Reaction with ester **4.47b** (29.8 mg, 0.0486 mmol) resulted in 11.4 mg of product as a white solid (69% yield) after purification via silica gel flash chromatography (40% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.18 (dd, *J* = 9.8, 5.9 Hz, 1H), 5.80 (dd, *J* = 9.8, 0.9 Hz, 1H), 5.56 – 5.29 (m, 2H), 4.66 (dt, *J* = 8.1, 3.8 Hz, 1H), 4.42 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.19 (d, *J* = 2.6 Hz, 1H), 3.12 (s, 3H), 2.78 (dd, *J* = 6.4, 4.3 Hz, 1H), 2.16 – 1.94 (m, 1H), 1.89 – 1.77 (m, 2H), 1.77 – 1.66 (m, 2H), 1.66 – 1.55 (m, 5H), 1.32 – 1.16 (m, 2H), 1.16 – 1.01 (m, 1H), 0.99 – 0.88 (m, 1H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 163.6, 149.9, 129.5, 126.9, 121.0, 91.0, 77.7, 67.2, 61.4, 39.6, 37.5, 37.5, 37.5, 36.5, 30.0, 19.9, 18.1, 15.5, 14.2, 11.8. HRMS calc *m/z* $[C_{20}H_{34}O_4 + Na]^+$: 361.2349, found: 361.2328. 98% pure by HPLC analysis.



4.44c

(*5R,6R*)-6-((*2R,3S,4R,5S,E*)-2-Hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5-(2,2,2-trifluoroethyl)-5,6-dihydro-2*H*-pyran-2-one (4.44c). Ester **4.47c** (20.8 mg, 0.0319 mmol) was dissolved in a hydrochloric acid/ethanol solution (1% HCl in ethanol, 0.8 mL) and stirred at room temperature overnight. The reaction was diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phase was washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity

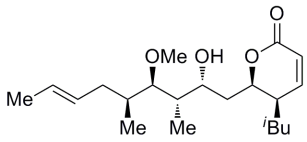
filtration and volatile materials were removed using a rotary evaporator. ^{19}F NMR spectroscopy of the crude material showed unreacted starting material. The crude material was resubmitted to the reaction conditions and stirred overnight. The reaction was diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phase was washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (5% to 15% EtOAc in DCM) to yield 6.52 mg of product as a white solid (54% yield). ^1H NMR (400 MHz, C_6D_6) δ 6.24 (ddt, *J* = 9.9, 6.3, 2.0 Hz, 1H), 5.70 (d, *J* = 9.8 Hz, 1H), 5.52 – 5.39 (m, 1H), 5.39 – 5.28 (m, 1H), 4.37 (dd, *J* = 8.2, 4.1 Hz, 1H), 4.17 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.17 (s, 1H), 3.06 (s, 3H), 2.69 (dd, *J* = 6.7, 3.9 Hz, 1H), 2.20 – 1.92 (m, 3H), 1.88 – 1.68 (m, 2H), 1.69 – 1.50 (m, 5H), 1.41 (ddd, *J* = 14.4, 10.1, 4.7 Hz, 1H), 1.26 (dd, *J* = 13.4, 9.5 Hz, 1H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.87 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 162.7, 147.5, 129.3, 127.1, 121.6, 91.2, 77.2, 67.2, 61.5, 39.4, 37.4, 37.3, 36.6, 32.3 (q, *J* = 28.1 Hz), 32.1 (d, *J* = 2.3 Hz), 18.2, 15.6, 11.9. Quaternary $-CF_3$ ^{13}C resonance not observed in spectrum. ^{19}F NMR (376 MHz, C_6D_6) δ -62.9. HRMS calc *m/z* $[C_{19}H_{29}F_3O_4 + Na]^+$: 401.1910, found: 401.1906. 95% pure by HPLC analysis.



4.44d

(*5R,6R*)-5-Cyclopropyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (4.44d). The product was synthesized following

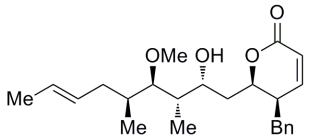
the procedure for the synthesis of analog **4.20**. Reaction with ester **4.47d** (44.7 mg, 0.0732 mmol) resulted in 18.0 mg of product as a white solid (73% yield) after purification via silica gel flash chromatography (45% to 50% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.09 (dd, *J* = 9.7, 5.9 Hz, 1H), 5.80 (dd, *J* = 9.7, 0.9 Hz, 1H), 5.54 – 5.30 (m, 2H), 4.67 (dt, *J* = 9.5, 3.3 Hz, 1H), 4.51 (dq, *J* = 9.6, 2.5 Hz, 1H), 3.17 (dd, *J* = 2.6, 1.3 Hz, 1H), 3.14 (s, 3H), 2.80 (dd, *J* = 6.3, 4.2 Hz, 1H), 2.18 – 2.03 (m, 1H), 1.94 – 1.71 (m, 5H), 1.68 – 1.58 (m, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.89 – 0.81 (m, 1H), 0.46 – 0.34 (m, 1H), 0.22 (dddd, *J* = 9.2, 7.9, 5.8, 4.4 Hz, 1H), 0.10 (dddd, *J* = 9.2, 8.1, 5.5, 4.4 Hz, 1H), -0.10 (dq, *J* = 9.8, 5.0 Hz, 1H), -0.29 (dq, *J* = 9.8, 5.0 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ 162.4, 147.1, 128.3, 125.7, 119.5, 89.9, 76.7, 65.9, 60.2, 41.1, 38.4, 36.8, 36.3, 35.3, 16.9, 14.3, 10.7, 7.4, 3.8, 0.0. HRMS calc *m/z* $[C_{20}H_{32}O_4 + Na]^+$: 359.2193, found: 359.2167. 97% pure by HPLC analysis.



4.44e

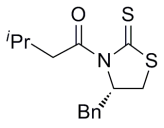
(*5R,6R*)-6-((*2R,3S,4R,5S,E*)-2-Hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5-isobutyl-5,6-dihydro-2*H*-pyran-2-one (4.44e). The product was synthesized following the procedure for the synthesis of analog **4.20**. Reaction with ester **4.47e** (23.0 mg, 0.0367 mmol) resulted in 7.57 mg of product as a white solid (59% yield) after purification via silica gel flash chromatography (35% EtOAc in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 6.19 (dd, *J* = 9.8, 6.0 Hz, 1H), 5.81 (dd, *J* = 9.8, 0.8 Hz, 1H), 5.54 – 5.29 (m, 2H), 4.68 (dt, *J* = 7.9, 3.8 Hz, 1H), 4.42 (d, *J* = 8.7 Hz, 1H), 3.18 (d, *J* = 1.9 Hz, 1H), 3.12 (s, 3H), 2.77 (dd, *J* = 6.4, 4.3 Hz, 1H), 2.16 – 1.99 (m, 1H), 1.93 – 1.76 (m, 3H),

1.75 – 1.67 (m, 1H), 1.67 – 1.56 (m, 5H), 1.32 – 1.21 (m, 2H), 1.14 (ddd, *J* = 13.6, 11.3, 4.8 Hz, 1H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.70 (d, *J* = 6.2 Hz, 3H), 0.65 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 163.6, 150.1, 129.5, 126.9, 120.9, 91.1, 77.9, 67.3, 61.4, 39.6, 37.5, 37.5, 36.8, 36.5, 35.6, 25.1, 24.0, 21.3, 18.1, 15.5, 11.8. HRMS calc *m/z* $[C_{21}H_{36}O_4 + Na]^+$: 375.2506, found: 375.2489. 93% pure by HPLC analysis.



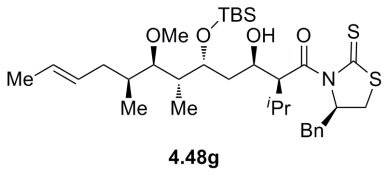
4.44f

(*5R,6R*)-5-Benzyl-6-((*2R,3S,4R,5S,E*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (4.44f). The product was synthesized following the procedure for the synthesis of analog **4.20**. Reaction with ester **4.47f** (25.8 mg, 0.0390 mmol) resulted in 6.52 mg of product as a colorless oil (43% yield) after purification via silica gel flash chromatography (20% acetone in hexanes followed by 4% EtOAc in DCM to 9% EtOAc in hexanes twice). ^{1}H NMR (400 MHz, C_6D_6) δ 7.13 – 7.00 (m, 3H), 6.93 – 6.76 (m, 2H), 5.96 (dd, *J* = 9.7, 5.9 Hz, 1H), 5.75 (d, *J* = 9.8 Hz, 1H), 5.60 – 5.27 (m, 2H), 4.61 (dt, *J* = 8.2, 3.9 Hz, 1H), 4.35 (dq, *J* = 9.8, 2.3 Hz, 1H), 3.22 (t, *J* = 1.7 Hz, 1H), 3.10 (s, 3H), 2.82 (dd, *J* = 12.9, 5.0 Hz, 1H), 2.75 (dd, *J* = 6.4, 4.2 Hz, 1H), 2.30 (dd, *J* = 12.9, 11.4 Hz, 1H), 2.22 – 1.98 (m, 2H), 1.88 – 1.75 (m, 2H), 1.75 – 1.57 (m, 6H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 163.5, 150.1, 138.8, 129.5, 129.3, 128.7, 127.0, 126.6, 121.0, 91.3, 77.9, 67.7, 61.4, 39.6, 39.5, 37.8, 37.5, 36.6, 34.1, 18.2, 15.6, 12.0. HRMS calc *m/z* $[C_{24}H_{34}O_4 + Na]^+$: 409.2349, found: 409.2345. 97% pure by HPLC analysis.



4.45g

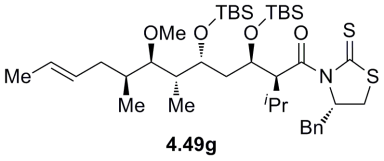
(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)-3-methylbutan-1-one (4.45g). The product was synthesized following the procedure for the synthesis of thiazolidinethione **4.39**. Reaction with (*S*)-4-benzylthiazolidine-2-thione (0.20 g, 0.96 mmol) and 3-methylbutyric chloride (0.12 mL, 1.0 mmol) resulted in 0.226 g of product as a yellow solid (81% yield) after purification via silica gel flash chromatography (40% to 50% DCM in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.38 (ddd, *J* = 10.8, 7.1, 3.9 Hz, 1H), 3.37 (dd, *J* = 11.5, 7.2 Hz, 1H), 3.28 – 2.99 (m, 4H), 2.87 (d, *J* = 11.5 Hz, 1H), 2.24 (dp, *J* = 13.4, 6.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 173.4, 136.6, 129.5, 128.9, 127.2, 68.6, 46.8, 36.8, 31.9, 25.3, 22.6, 22.3. $[\alpha]_D$ = +234 (*c* 0.188, $CHCl_3$). HRMS calc *m/z* $[C_{15}H_{19}NOS_2 + Na]^+$: 316.0800, found: 316.0844.



4.48g

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-isopropyl-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.48g). The product was synthesized following the procedure for the synthesis of intermediate **4.40**. Reaction with thiazolidinethione **4.45g** (0.137 g, 0.467 mmol) and aldehyde **4.25** (46.4 mg, 0.135 mmol) resulted in 65.7 mg of product as a yellow oil (76% yield) after purification via silica gel flash chromatography (10% EtOAc in hexanes). ^{1}H

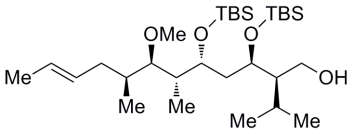
NMR (400 MHz, C_6D_6) δ 7.14 – 6.96 (m, 5H), 5.53 – 5.37 (m, 3H), 5.26 (ddd, *J* = 10.7, 7.1, 3.7 Hz, 1H), 4.38 – 4.20 (m, 2H), 3.40 (s, 3H), 3.23 (dd, *J* = 8.7, 2.0 Hz, 1H), 3.12 (dd, *J* = 13.1, 3.7 Hz, 1H), 2.74 (dd, *J* = 13.1, 10.7 Hz, 1H), 2.56 (dd, *J* = 11.5, 7.2 Hz, 1H), 2.44 (bs, 1H), 2.42 – 2.32 (m, 1H), 2.32 – 2.17 (m, 1H), 2.15 – 1.91 (m, 5H), 1.82 – 1.68 (m, 1H), 1.64 (d, *J* = 4.2 Hz, 3H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.04 – 0.98 (m, 12H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.23 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 202.7, 175.9, 137.1, 130.9, 129.7, 128.9, 128.5, 127.2, 126.5, 84.9, 72.1, 70.4, 69.4, 60.4, 54.6, 41.7, 39.1, 39.0, 37.0, 36.1, 31.2, 29.3, 26.3, 21.8, 20.1, 18.6, 18.2, 13.6, 11.5, -3.4, -4.0. HRMS calc *m/z* $[C_{34}H_{57}NO_4S_2Si + Na]^+$: 658.3390, found: 658.3448.



4.49g

(*2S,3R,5R,6R,7R,8S,E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-isopropyl-7-methoxy-6,8-dimethyldodec-10-en-1-one (4.49g). The product was synthesized following the procedure for the synthesis of intermediate **4.49b**. Reaction with alcohol **4.48g** (68.7 mg, 0.108 mmol) resulted in 75.4 mg of product as a yellow oil (93% yield) after purification via silica gel flash chromatography (100:3 hexanes:EtOAc followed by 4% ether in hexanes). ^{1}H NMR (400 MHz, C_6D_6) δ 7.14 – 6.99 (m, 5H), 5.52 – 5.40 (m, 2H), 5.36 (dd, *J* = 9.8, 3.9 Hz, 1H), 5.23 (ddd, *J* = 10.6, 6.9, 3.4 Hz, 1H), 4.49 (dd, *J* = 9.2, 4.4 Hz, 1H), 4.27 (dt, *J* = 7.1, 4.5 Hz, 1H), 3.51 (s, 3H), 3.35 (dd, *J* = 9.7, 1.6 Hz, 1H), 3.25 (dd, *J* = 13.0, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.1, 10.9 Hz, 1H), 2.69 (dd, *J* = 11.5, 7.0 Hz, 1H), 2.59 – 2.39 (m,

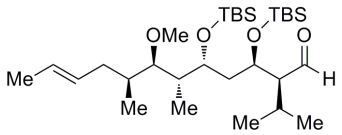
2H), 2.35 – 2.20 (m, 1H), 2.18 – 2.04 (m, 3H), 1.90 – 1.79 (m, 1H), 1.76 (q, *J* = 7.0 Hz, 1H), 1.69 – 1.62 (m, 3H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 9H), 1.02 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.38 (s, 3H), 0.35 (s, 3H), 0.29 (s, 3H), 0.23 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 201.9, 176.1, 137.3, 131.1, 129.8, 129.0, 128.6, 127.2, 126.5, 84.2, 71.4, 70.1, 70.0, 61.1, 56.0, 42.8, 41.5, 39.0, 36.7, 36.3, 31.2, 29.3, 26.4, 26.3, 21.6, 21.3, 18.8, 18.3, 18.2, 13.1, 10.4, -2.3, -3.7, -3.7, -4.3. HRMS calc *m/z* $[C_{40}H_{71}NO_4S_2Si_2 + Na]^+$: 772.4261, found: 772.4287.



4.50

(*2R,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-isopropyl-7-methoxy-6,8-dimethyldodec-10-en-1-ol (4.50). To a solution of amide **4.49g** (39.4 mg, 0.0525 mmol) in ether (15 mL) and MeOH (0.03 mL) at 0 °C was added $LiBH_4$ (2 M in THF, 58 µL, 0.120 mmol). The reaction was stirred at 0 °C for 3 h before additional $LiBH_4$ (2 M in THF, 58 µL, 0.120 mmol) was added to the reaction. The reaction was stirred at 0 °C for an addition 2 h before additional $LiBH_4$ (2 M in THF, 58 µL, 0.120 mmol) was added to the reaction. The reaction was then stored in a 4 °C refrigerator overnight. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (10% EtOAc in hexanes) to yield 17.1 mg of product as a colorless oil (60% yield) and 11.9 mg of recovered starting material. ^{1}H NMR (400 MHz, C_6D_6) δ

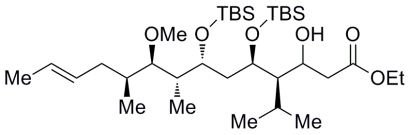
5.51 – 5.34 (m, 2H), 4.29 (ddd, *J* = 8.5, 6.1, 2.1 Hz, 1H), 4.22 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.67 (d, *J* = 6.7 Hz, 2H), 3.45 (s, 3H), 3.31 (dd, *J* = 9.8, 1.6 Hz, 1H), 2.30 – 2.18 (m, 1H), 2.17 – 1.99 (m, 4H), 1.83 (dq, *J* = 9.6, 6.9 Hz, 1H), 1.73 (q, *J* = 7.7, 7.0 Hz, 1H), 1.68 – 1.62 (m, 3H), 1.62 – 1.54 (m, 1H), 1.42 (bs, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 9H), 1.01 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.22 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 131.0, 126.4, 84.3, 70.1, 70.0, 61.0, 60.3, 49.4, 40.6, 40.1, 38.9, 36.1, 26.3, 26.2, 25.7, 23.5, 19.9, 18.6, 18.3, 18.2, 13.0, 9.7, -2.7, -4.2, -4.2, -4.3. HRMS calc *m/z* [$C_{30}H_{64}O_4Si_2$ + Na]$^+$: 567.4235, found: 567.4224.



4.46g

(*2S,3R,5R,6R,7R,8S,E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-2-isopropyl-7-methoxy-6,8-dimethyldodec-10-enal (4.46g). To a suspension of alcohol **4.50** (26.0 mg, 0.0477 mmol) and powdered 4Å molecular sieves (11 mg) in DCM (0.6 mL) at 0 °C was added a solution of TPAP (1.7 mg, 4.8 μmol) in DCM (0.2 mL). The reaction was stirred for 30 min at 0 °C followed by addition of NMO (7.3 mg, 0.062 mmol). After stirring an additional 1 h at 0 °C, additional NMO (7.3 mg, 0.062 mmol) was added to the reaction followed by a solution of TPAP (1.7 mg, 4.8 μmol) in DCM (0.2 mL). After the reaction was judged to be complete via TLC analysis, silica gel was added to the reaction and volatile materials were removed using a rotary evaporator. Purification via silica gel flash chromatography (5% EtOAc in hexanes) yielded 19.2 mg of product as a colorless oil (74% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 9.84 (d, *J* = 2.6 Hz, 1H), 5.55 – 5.33 (m,

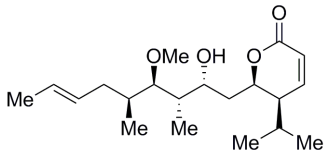
2H), 4.35 (td, *J* = 6.7, 3.6 Hz, 1H), 4.26 – 4.14 (m, 2H), 3.42 (s, 3H), 3.26 (dd, *J* = 9.7, 1.7 Hz, 1H), 2.30 (ddd, *J* = 6.4, 3.7, 2.6 Hz, 1H), 2.28 – 2.14 (m, 2H), 2.15 – 1.92 (m, 3H), 1.81 – 1.67 (m, 2H), 1.65 (d, *J* = 3.9 Hz, 3H), 1.07 (dd, *J* = 6.8, 1.1 Hz, 6H), 1.00 (s, 9H), 0.99 – 0.94 (m, 12H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.19 (s, 3H), 0.17 (s, 6H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 203.4, 131.0, 126.5, 84.0, 70.3, 70.0, 62.4, 60.9, 41.1, 41.1, 38.9, 36.1, 26.2, 26.1, 25.6, 21.9, 20.7, 18.6, 18.2, 13.1, 9.9, -2.8, -4.0, -4.1, -4.2. HRMS calc *m/z* $[C_{30}H_{62}O_4Si_2 + Na]^+$: 565.4079, found: 565.4053.



4.51

(*4R,5R,7R,8R,9R,10S,E*)-Ethyl 5,7-Bis((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-isopropyl-9-methoxy-8,10-dimethyltetradec-12-enoate (4.51). To THF (0.5 mL) at 0 °C was added lithium bis(trimethylsilyl)amide (1 M in hexanes, 0.062 mL, 0.062 mmol). The solution was stirred at 0 °C for 15 min before cooling to -78 °C. Ethyl acetate (5.6 μL, 0.057 mmol) was added dropwise to the reaction and the reaction was stirred at -78 °C for 30 min. A solution of aldehyde **4.46g** (22.3 mg, 0.0411 mmol) dissolved in THF (0.5 mL) was slowly cannula transferred to the reaction. The vial containing the aldehyde solution was rinsed with additional THF (0.5 mL) which was cannula transferred to the reaction. After stirring for 15 min at -78 °C, the reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The layers were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary

evaporator. The crude material was purified via silica gel flash chromatography (10% EtOAc in hexanes) to yield 18.9 mg of product as a colorless oil (73% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 5.52 – 5.30 (m, 2H), 4.69 (t, *J* = 8.2 Hz, 1H), 4.22 (dd, *J* = 10.7, 4.3 Hz, 1H), 4.17 (dd, *J* = 9.6, 5.2 Hz, 1H), 4.02 – 3.83 (m, 2H), 3.40 (s, 3H), 3.28 (dd, *J* = 9.8, 1.6 Hz, 1H), 3.13 (bs, 1H), 2.75 (dd, *J* = 16.0, 2.5 Hz, 1H), 2.65 (dd, *J* = 16.0, 9.9 Hz, 1H), 2.35 – 2.12 (m, 3H), 2.12 – 1.98 (m, 2H), 1.87 (dt, *J* = 9.1, 6.9 Hz, 1H), 1.71 (q, *J* = 6.9 Hz, 1H), 1.68 – 1.59 (m, 4H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.04 – 0.95 (m, 21H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.22 (s, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 173.1, 131.0, 126.5, 84.4, 69.8, 69.7, 68.3, 61.1, 60.5, 52.0, 42.0, 39.9, 39.5, 38.8, 36.1, 26.4, 26.2, 26.2, 24.8, 21.0, 18.5, 18.3, 18.2, 14.1, 13.0, 9.6, -2.8, -3.5, -4.2, -4.3. HRMS calc *m/z* [$C_{34}H_{70}O_6Si_2$ + Na]$^+$: 653.4603, found: 653.4624.



4.44g

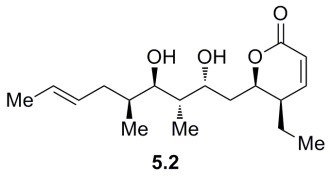
(*5R,6R*)-6-((*2R,3S,4R,5S,E*)-2-Hydroxy-4-methoxy-3,5-dimethylnon-7-en-1-yl)-5-isopropyl-5,6-dihydro-2*H*-pyran-2-one (4.44g). To an NMR tube containing *p*-toluenesulfonic acid monohydrate (5.7 mg, 0.030 mmol) was added a solution of ester **4.51** (18.2 mg, 0.0288 mmol) dissolved in d_8-toluene (1 mL). The reaction was heated to 110 °C in an oil bath and monitored by ^{1}H NMR spectroscopy. After heating for 1.5 h, additional *p*-toluenesulfonic acid monohydrate (5.7 mg, 0.030 mmol) was added to the reaction followed by d_8-toluene (50 µL). The reaction was heated to 110 °C for an

additional 2.5 h and judged to be complete by ^{1}H NMR spectroscopy. The reaction was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine before drying with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (20% acetone in hexanes) to yield 6.6 mg of product as a white solid (65% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.88 (dd, *J* = 9.9, 5.8 Hz, 1H), 6.07 (dd, *J* = 9.9, 1.3 Hz, 1H), 5.58 – 5.35 (m, 2H), 4.83 – 4.67 (m, 1H), 4.16 (t, *J* = 6.7 Hz, 1H), 3.47 (s, 3H), 3.21 (d, *J* = 2.5 Hz, 1H), 3.01 (dd, *J* = 6.0, 4.7 Hz, 1H), 2.34 (dtd, *J* = 5.8, 4.5, 1.3 Hz, 1H), 2.25 – 2.06 (m, 2H), 1.95 – 1.82 (m, 2H), 1.82 – 1.75 (m, 1H), 1.75 – 1.70 (m, 2H), 1.70 – 1.62 (m, 3H), 0.98 (d, *J* = 7.1 Hz, 6H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 164.8, 147.6, 129.6, 127.3, 122.9, 91.2, 78.2, 67.7, 62.0, 43.8, 39.7, 37.8, 37.0, 36.8, 27.9, 21.6, 18.3, 18.3, 15.4, 12.3. HRMS calc *m/z* $[C_{20}H_{34}O_4 + Na]^+$: 361.2349, found: 361.2398. 95% pure by HPLC analysis,

6.4.2 Covalent docking protocol. Pironetin and related analogs were docked using Schrödinger® Maestro software package. α-Tubulin was selected from previously reported pironetin crystal structure (chain C of PDB ID 5FNV). Following removal of the pironetin from the protein, the protein was prepared via Protein Preparation Wizard. Poses for each ligand were prepared using the Ligprep module using an OLPS3 force field. Pironetin analogs were docked into the prepared α-tubulin using Glide CovDoc module. The binding site was centered at Cys316 and docking poses were generated for covalent adducts resulting from the Michael addition of Cys316 into each analog. Ten

poses were obtained for each analog and each pose was given a separate docking score, glide score and Cdcok affinity.

6.5 Chapter 5 experimental procedures.



5.2

(*5R,6R*)-6-((*2R,3S,4R,5S,E*)-2,4-Dihydroxy-3,5-dimethylnon-7-en-1-yl)-5-ethyl-5,6-dihydro-2*H*-pyran-2-one/ Demethylpironetin/NK10958P (5.2). Demethyl pironetin was isolated from the combination of the three following reactions conditions: The reaction conditions were adapted from previously a published reaction.[52]

Reaction 1. To a solution of pironetin (8.7 mg, 0.027 mmol) in DCM (1.4 mL) at -78 °C was added a 15-crown-5 solution (0.3 M in DCM, 0.54 mL, 0.16 mmol) saturated with sodium iodide. BBr_3 (1 M in DCM, 80 µL, 0.080 mmol) was subsequently added dropwise to the reaction at -78 °C. The reaction was warmed to 0 °C over 3 h and stirred at 0 °C for 3 h. The reaction was diluted with diethyl ether and quenched with saturated aqueous NH_4Cl and saturated sodium thiosulfate solutions. The layers were separated and the aqueous layer was extract four times with ether. The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was frozen in benzene prior to purification.

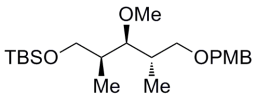
Reaction 2. To a solution of pironetin (3.4 mg, 0.010 mmol) in DCM (0.5 mL) at -78 °C was added a 15-crown-5 solution (0.3 M in DCM, 0.20 mL, 0.060 mmol) saturated with sodium iodide. BBr_3 (1 M in DCM, 30 µL, 0.030 mmol) was added dropwise to the

reaction at -78 °C. The reaction was warmed to 0 °C over 3 h and stirred at 0 °C for 3 h. The reaction was diluted with diethyl ether and quenched with saturated aqueous NH_4Cl and saturated sodium thiosulfate solutions. The layers were separated and aqueous layer was extract four times with ether. The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was frozen in benzene prior to purification.

Reaction 3. To a solution of pironetin (5.2 mg, 0.016 mmol) in DCM (0.5 mL) at -30 °C (ethanol/ice bath) was added a 15-crown-5 solution (0.3 M in DCM, 0.33 mL, 0.099 mmol) saturated with sodium iodide. BBr_3 (1 M in DCM, 50 µL, 0.050 mmol) was subsequently added dropwise to the reaction at -30 °C. After 1.5 h at -30 °C, the reaction was quenched with saturated aqueous NH_4Cl and saturated sodium thiosulfate solutions. The layers were separated and aqueous layer was extract four times with ethyl acetate. The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was frozen in benzene prior to purification.

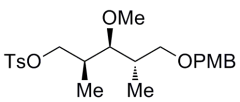
The combined crude material from these three reactions was purified by silica gel flash chromatography through the following series of solvent mixtures: 30% to 50% ethyl acetate in hexanes, 50% ethyl acetate in hexanes (three times). 2.2 mg of demethyl pironetin was isolated as a color oil resulting in 13% yield from the combined amount of pironetin used for the three reactions. The resonances in the ^{1}H NMR and ^{13}C spectrum

of the product matched previously reported chemical shifts.[52,112] 86% pure by HPLC analysis.



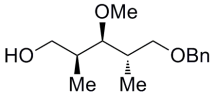
5.16b

***tert*-Butyl(((*2S,3S,4S*)-3-methoxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentyl)oxy)dimethylsilane (5.16b).** To a solution of alcohol **5.17** (0.61 g, 2.2 mmol) in DMF (6.3 mL) at 0 °C was added sodium hydride (60% in mineral oil, 0.17 g, 4.2 mmol). The suspension was stirred at 0 °C for 20 min before the addition of PMBCl (0.57 mL, 4.2 mmol). The reaction was warmed to room temperature and stirred for 4.5 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via Combiflash® silica gel flash chromatograph (5% to 100% EtOAc in hexanes) to yield 0.51 g of product as a colorless oil (59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 6.91 – 6.84 (m, 2H), 4.54 – 4.37 (m, 2H), 3.80 (s, 3H), 3.62 – 3.51 (m, 2H), 3.45 (ddd, *J* = 12.9, 9.3, 6.4 Hz, 2H), 3.38 (s, 3H), 3.25 (dd, *J* = 8.9, 2.8 Hz, 1H), 2.00 – 1.88 (m, 1H), 1.88 – 1.75 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 131.0, 129.0, 113.7, 82.1, 72.7, 72.6, 65.7, 60.8, 55.2, 37.8, 36.8, 25.9, 25.9, 18.2, 14.8, 9.9, -5.3.



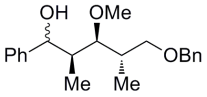
5.18

(*2S,3S,4S*)-3-Methoxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentyl 4-methylbenzenesulfonate (5.18). To a solution of ether **5.16b** (0.51 g, 1.3 mmol) in THF (2.1 mL) was added TBAF (1 M in THF, 6.4 mL, 6.4 mmol). After stirring for 2.5 h, the reaction was diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was dissolved in pyridine (8.6 mL) followed by the addition of TsCl (0.74 g, 3.9 mmol). The reaction was stirred overnight and then poured into water and diluted with ether. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via Combiflash® silica gel flash chromatograph (5% to 20% EtOAc in hexanes) to yield 0.48 g of product as a colorless oil (85% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.74 (m, 2H), 7.37 – 7.30 (m, 2H), 7.27 – 7.20 (m, 2H), 6.92 – 6.84 (m, 2H), 4.41 (s, 2H), 4.00 (dd, *J* = 9.3, 8.1 Hz, 1H), 3.90 (dd, *J* = 9.4, 6.0 Hz, 1H), 3.81 (s, 3H), 3.50 – 3.35 (m, 2H), 3.27 (s, 3H), 3.14 (dd, *J* = 8.9, 2.8 Hz, 1H), 2.44 (s, 3H), 2.10 – 1.94 (m, 2H), 1.91 – 1.76 (m, 1H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 144.7, 133.1, 130.6, 129.8, 129.2, 127.9, 113.7, 81.3, 72.8, 72.7, 71.9, 60.8, 55.2, 36.6, 35.0, 21.7, 14.5, 9.6.



5.20a

(*2S,3R,4S*)-5-(Benzyloxy)-3-methoxy-2,4-dimethylpentan-1-ol (5.20a). To a solution of ether **5.16a** (0.10 g, 0.27 mmol) in THF (0.45 mL) was added TBAF (1 M in THF, 1.4 mL, 1.4 mmol). After stirring for 3.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (33% EtOAc in hexanes) to yield 67.3 mg of product as a colorless oil (98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.32 – 7.25 (m, 1H), 4.51 (s, 2H), 3.63 (t, *J* = 5.5 Hz, 2H), 3.61 – 3.44 (m, 2H), 3.41 (s, 3H), 3.27 (dd, *J* = 8.4, 3.1 Hz, 1H), 2.06 – 1.92 (m, 1H), 1.95 – 1.82 (m, 2H), 1.29 – 1.16 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 83.9, 73.1, 72.5, 66.6, 60.6, 37.4, 36.6, 14.8, 10.5. HRMS calc *m/z* $[C_{15}H_{24}O_3 + Na]^+$: 275.1618, found: 275.1632.

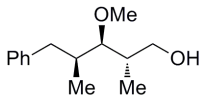


5.22a

(*2S,3S,4S*)-5-(Benzyloxy)-3-methoxy-2,4-dimethyl-1-phenylpentan-1-ol (5.22a). A suspension of alcohol **5.20a** (50. mg, 0.20 mmol), NMO (28 mg, 0.24 mmol), and powdered 4Å molecular sieves (55 mg) was stirred in DCM (1.8 mL) at 0 °C for 20 min. A solution of TPAP (7 mg, 0.02 mmol) in DCM (0.5 mL) was added to the reaction. The

reaction was warmed to room temperature and stirred for 45 min. The reaction was diluted with 40% EtOAc in hexanes and filtered through a plug of silica gel. The silica gel plug was rinsed with 40% acetate in hexanes. The solution of crude material was concentrated using a rotary evaporator and the crude aldehyde was used without further purification.

To a solution of the crude aldehyde in THF (2 mL) at -78 °C was added phenylmagnesium bromide (2.8 M in ether, 0.10 mL, 0.28 mmol). After stirring at -78 °C for 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was warmed to room temperature and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (12% EtOAc in hexanes) to yield 41.9 mg of product as a colorless oil (64% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (q, *J* = 4.1 Hz, 16H), 7.30 – 7.21 (m, 4H), 4.97 (d, *J* = 2.8 Hz, 1H), 4.58 (dd, *J* = 8.4, 3.8 Hz, 1H), 4.57 – 4.46 (m, 4H), 3.64 – 3.54 (m, 3H), 3.54 – 3.44 (m, 9H), 2.66 (d, *J* = 3.9 Hz, 1H), 2.17 – 1.90 (m, 4H), 0.97 (dd, *J* = 7.0, 4.6 Hz, 6H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.6, 138.6, 138.4, 128.4, 128.4, 128.3, 128.1, 127.6, 127.6, 127.5, 127.5, 127.4, 126.9, 126.6, 126.0, 87.2, 82.0, 77.5, 73.2, 73.1, 72.8, 72.2, 60.1, 60.0, 41.5, 41.4, 36.7, 36.7, 14.6, 14.5, 10.8, 6.0. HRMS calc *m/z* $[C_{21}H_{28}O_3 + Na]^+$: 351.1931, found: 351.1947.

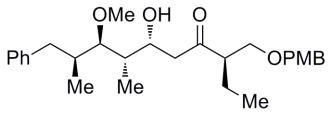


5.15

(*2S,3R,4S*)-3-Methoxy-2,4-dimethyl-5-phenylpentan-1-ol (5.15). To a solution of alcohol **5.22a** (32 mg, 0.097 mmol) and DMAP (2.4 mg, 0.019 mmol) in DCM (2 mL) at 0 °C was added trifluoroacetic anhydride (0.035 mL, 0.25 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and warmed to room temperature. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was dissolved in 30% EtOAc in hexanes and filtered through a plug of silica gel. The silica gel plug was rinsed with 30% EtOAc in hexanes. The crude trifluoroacetate ester solution was concentrated using a rotary evaporator; the crude material was used without further purification.

To a solution of the crude material dissolved in EtOAc (1 mL) was added palladium (10% on carbon, 10. mg, 0.0097mmol). The reaction was placed under a balloon of H_2 and stirred at room temperature overnight. The reaction was filtered through a Celite® plug and the Celite® plug was rinsed with EtOAc. The solution of the crude material was concentrated using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (35% EtOAc in hexanes) to yield 17.2 mg of product as a colorless oil (80% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 2H), 7.20 – 7.09 (m, 3H), 3.61 (d, J = 5.2 Hz, 2H), 3.49 (s, 3H), 3.00 (dd, J = 7.9, 3.2 Hz, 1H), 2.76 (dd, J = 13.4, 5.7 Hz, 1H), 2.68 (s, 1H), 2.49 (dd, J = 13.4, 9.2 Hz, 1H), 2.00

(tq, J = 9.3, 3.1 Hz, 1H), 1.88 (ddt, J = 9.5, 7.3, 3.6 Hz, 1H), 0.86 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 129.0, 128.3, 125.9, 90.0, 66.7, 61.2, 40.8, 37.9, 37.8, 15.1, 13.4. HRMS calc m/z $[C_{14}H_{22}O_2 + Na]^+$: 245.1512, found: 245.1525.

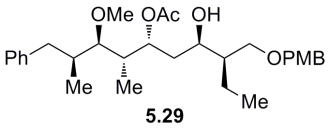


5.28

(*3R,6R,7S,8R,9S*)-6-Hydroxy-8-methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-dimethyl-10-phenyldecan-4-one (5.28). A suspension of alcohol **5.15** (64.1 mg, 0.288 mmol), NMO (44 mg, 0.38 mmol), and powdered 4Å molecular sieves (79 mg) was stirred in DCM (2 mL) at 0 °C for 15 min. A solution of TPAP (10. mg, 0.029 mmol) in DCM (0.6 mL) was added to the reaction. After stirring at 0 °C for 40 min, the reaction was diluted with 40% EtOAc in hexanes and filtered through a plug of silica gel. The silica gel plug was rinsed with 40% acetate in hexanes. The crude aldehyde solution was concentrated using a rotary evaporator and the crude aldehyde was used without further purification.

The crude aldehyde was combined with crude silyl enol ethers **5.27** (~0.57 mmol) and dissolved in DCM (2.6 mL) and cooled in a MeOH/*lq* N_2 bath. A solution of BF_3•Et_2O (2M in DCM, 0.36 mL, 0.72 mmol) was added dropwise and the reaction was stirred in the MeOH/*lq* N2 bath for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and warmed to room temperature. The layers were separated and the aqueous phase was extracted three times with DCM and once with EtOAc. The combined organic extracts were washed with brine and dry with anhydrous Na_2SO_4. The

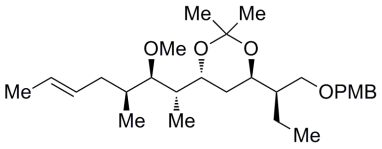
salts were removed via gravity filtration and volatile materials were removed by rotary evaporator. The crude material was purified via silica gel flash chromatography (20% EtOAc in hexanes) to yield 76.3 mg of product as a colorless oil (58% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.14 (m, 5H), 6.90 – 6.77 (m, 2H), 4.47 (d, *J* = 8.4 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 3.59 (t, *J* = 8.8 Hz, 1H), 3.52 (s, 3H), 3.49 (dd, *J* = 9.1, 5.0 Hz, 1H), 3.35 (d, *J* = 2.5 Hz, 1H), 3.18 (dd, *J* = 7.9, 3.6 Hz, 1H), 2.90 – 2.68 (m, 3H), 2.56 – 2.41 (m, 2H), 2.04 (dq, *J* = 9.9, 4.5 Hz, 1H), 1.63 (ddt, *J* = 11.0, 7.6, 5.6 Hz, 2H), 1.51 – 1.37 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 159.2, 141.2, 129.9, 129.3, 129.1, 128.2, 125.7, 113.7, 87.1, 72.9, 70.5, 66.5, 61.6, 55.2, 54.3, 48.1, 40.9, 40.0, 37.5, 21.5, 12.7, 11.7, 10.4. HRMS calc *m/z* $[C_{28}H_{40}O_5 + Na]^+$: 479.2768, found: 479.2854.



5.29

(*2S,3R,4S,5R,7R,8R*)-7-Hydroxy-3-methoxy-8-(((4-methoxybenzyl)oxy)methyl)-2,4-dimethyl-1-phenyldecan-5-yl Acetate (5.29). To a solution of ketone **5.28** (76.3 mg, 0.167 mmol) and acetaldehyde (0.075 mL, 1.3 mmol) in THF (0.7 mL) at -15 °C was added dropwise a solution of SmI_2 (0.06 M in THF, 1.1 mL, 0.067 mmol). The reaction was stirred at -15 °C for 1 h before quenching with saturated aqueous $NaHCO_3$. The mixture was warmed to room temperature and extracted four times with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a

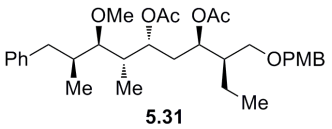
rotary evaporator. The crude material was initially purified via silica gel flash chromatograph (4:1 hexanes:EtOAc). The impure product was subsequently purified via silica gel flash chromatograph (25% EtOAc in hexanes twice) to yield 76.1 mg of product as a colorless oil (91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, 7H), 6.91 – 6.81 (m, 2H), 5.40 (ddd, *J* = 9.6, 3.9, 2.0 Hz, 1H), 4.51 – 4.31 (ABq, 2H), 3.80 (s, 3H), 3.67 (dt, *J* = 10.5, 3.0 Hz, 1H), 3.56 – 3.45 (m, 2H), 3.44 (s, 3H), 2.89 (dd, *J* = 9.4, 2.0 Hz, 1H), 2.78 (dd, *J* = 13.4, 5.4 Hz, 1H), 2.59 (dd, *J* = 13.3, 9.5 Hz, 1H), 2.05 (s, 3H), 2.03 – 1.92 (m, 1H), 1.83 – 1.64 (m, 2H), 1.56 (tdd, *J* = 14.1, 9.4, 4.0 Hz, 2H), 1.49 – 1.29 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 159.1, 141.3, 130.4, 129.2, 129.1, 128.2, 125.8, 113.7, 85.5, 72.9, 71.8, 70.7, 68.7, 61.4, 55.3, 45.5, 41.6, 40.3, 37.6, 37.4, 21.2, 19.1, 12.4, 12.1, 10.5. HRMS calc *m/z* $[C_{30}H_{44}O_6 + Na]^+$: 523.3030, found: 523.3085.



5.30

(*4R,6R*)-4-((*2S,3R,4S,E*)-3-Methoxy-4-methyloct-6-en-2-yl)-6-((*R*)-1-((4-methoxybenzyl)oxy)butan-2-yl)-2,2-dimethyl-1,3-dioxane (5.30). To a solution of alcohol **5.29** (7.0 mg, 0.014 mmol) in methanol (0.55 mL) was added potassium hydroxide (4 mg, 0.07 mmol). The reaction was stirred at room temperature for 3.5 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted four times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude diol was stirred overnight in 2,2-

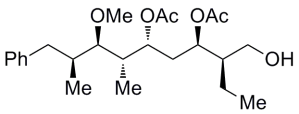
dimethoxypropane (1 mL) with PPTS (1 mg). The reaction was diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatograph (7% EtOAc in hexanes) to yield 4.1 mg of product as a colorless oil (59% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.11 (m, 7H), 6.91 – 6.82 (m, 2H), 4.47 – 4.33 (ABq, 2H), 4.06 (ddd, *J* = 9.1, 6.9, 2.7 Hz, 1H), 3.80 (s, 3H), 3.83 – 3.74 (m, 1H), 3.52 (s, 3H), 3.47 – 3.29 (m, 2H), 3.15 (dd, *J* = 9.1, 1.9 Hz, 1H), 2.82 (dd, *J* = 13.2, 5.0 Hz, 1H), 2.57 (dd, *J* = 13.2, 9.7 Hz, 1H), 1.97 (q, *J* = 6.1 Hz, 1H), 1.68 – 1.43 (m, 5H), 1.41 (s, 1H), 1.35 (s, 3H), 1.29 (s, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 141.5, 130.7, 129.3, 129.2, 129.1, 128.2, 128.2, 125.7, 113.8, 113.7, 100.0, 85.3, 72.8, 68.4, 67.2, 65.6, 61.0, 55.2, 45.0, 41.9, 41.0, 37.6, 33.9, 25.0, 24.8, 20.0, 12.1, 11.7, 10.2. HRMS calc *m/z* $[C_{31}H_{46}O_5 + Na]^+$: 521.3237, found: 521.3203 + 481.2931 (hydrolyzed acetonide).



5.31

(*3R,4R,6R,7S,8R,9S*)-8-Methoxy-3-(((4-methoxybenzyl)oxy)methyl)-7,9-dimethyl-10-phenyldecane-4,6-diyl Diacetate (5.31). To solution of alcohol **5.29** (67.7 mg, 0.135 mmol) in DCM (1 mL) was added TEA (0.34 mL, 2.4 mmol), Ac_2O (0.23 mL, 2.4 mmol) followed by DMAP (1 mg, 0.06 mmol). The reaction was stirred overnight. The reaction

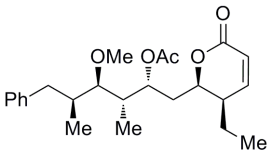
was diluted with DCM and quenched with saturated aqueous $NaHCO_3$ (10 mL). The biphasic mixture was stirred for 2.5 h. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (20% EtOAc in hexanes) to yield 64.5 mg of product as a colorless oil (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 4H), 7.22 – 7.12 (m, 3H), 6.89 – 6.82 (m, 2H), 5.25 (ddd, *J* = 9.3, 4.5, 2.1 Hz, 1H), 5.03 (dt, *J* = 10.2, 3.9 Hz, 1H), 4.39 (s, 2H), 3.79 (s, 3H), 3.50 (s, 3H), 3.45 – 3.27 (m, 2H), 2.92 (dd, *J* = 9.3, 2.0 Hz, 1H), 2.78 (dd, *J* = 13.3, 5.1 Hz, 1H), 2.56 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 – 1.89 (m, 1H), 1.85 (ddd, *J* = 13.4, 9.3, 3.7 Hz, 1H), 1.80 – 1.63 (m, 3H), 1.41 (p, *J* = 7.3 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 159.0, 141.2, 130.7, 129.1, 129.1, 129.1, 128.2, 125.8, 113.6, 85.6, 72.7, 71.1, 70.1, 69.1, 61.2, 55.2, 43.7, 41.6, 40.4, 37.4, 34.4, 21.1, 21.0, 20.2, 12.0, 10.6. HRMS calc *m/z* [$C_{32}H_{46}O_7$ + Na]$^+$: 565.3136, found: 565.3164.



5.32

(*3R,4R,6R,7S,8R,9S*)-3-(Hydroxymethyl)-8-methoxy-7,9-dimethyl-10-phenyldecane-4,6-diyl Diacetate (5.32). To a solution of ester **5.31** (63.9 mg, 0.118 mmol) in DCM (1 mL) and water (0.09 mL) was added DDQ (67 mg, 0.29 mmol). After stirring at room temperature for 30 min, the reaction was diluted with DCM and quenched with saturated

aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phase was washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was purified via silica gel flash chromatography (30% EtOAc in hexanes) to yield 40.9 mg of product as a colorless oil (82% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.32 – 7.24 (m, 2H), 7.22 – 7.13 (m, 3H), 5.25 (ddd, *J* = 9.3, 4.2, 2.2 Hz, 1H), 5.03 (dt, *J* = 10.6, 2.9 Hz, 1H), 3.58 (ddd, *J* = 12.6, 8.4, 4.9 Hz, 1H), 3.46 (s, 3H), 3.25 (ddd, *J* = 12.1, 9.0, 3.9 Hz, 1H), 2.89 (dd, *J* = 9.2, 2.2 Hz, 1H), 2.78 (dd, *J* = 13.3, 5.3 Hz, 1H), 2.66 (dd, *J* = 8.9, 4.8 Hz, 1H), 2.56 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.05 (s, 3H), 1.98 (s, 3H), 2.01 – 1.93 (m, 1H) 1.88 (ddd, *J* = 14.7, 10.6, 4.2 Hz, 1H), 1.75 (ddd, *J* = 14.5, 9.4, 3.2 Hz, 1H), 1.68 (ddd, *J* = 9.2, 7.1, 2.2 Hz, 1H), 1.63 – 1.52 (m, 1H), 1.45 (dtd, *J* = 15.0, 7.4, 4.3 Hz, 1H), 1.14 (ddt, *J* = 14.2, 8.6, 7.2 Hz, 1H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 172.7, 171.1, 142.0, 129.6, 128.7, 126.3, 86.0, 70.9, 70.6, 62.2, 61.5, 46.9, 42.1, 41.0, 38.0, 35.9, 21.4, 21.4, 19.2, 12.6, 12.5, 10.9. HRMS calc *m/z* $[C_{24}H_{38}O_6 + Na]^+$: 445.2561, found: 445.2596.



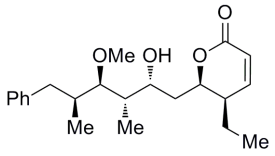
5.33

(*2R,3S,4R,5S*)-1-((*2R,3R*)-3-Ethyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-4-methoxy-3,5-dimethyl-6-phenylhexan-2-yl Acetate (5.33). A suspension of alcohol **5.32** (40.9 mg, 0.0968 mmol), NMO (17 mg, 0.15 mmol), and powdered 4Å molecular sieves (47 mg)

was stirred in DCM (1.6 mL) at 0 °C for 15 min. A solution of TPAP (3.4 mg, 0.0097 mmol) in DCM (0.3 mL) was added to the reaction. After stirring 40 min at 0 °C, the reaction was diluted with 40% EtOAc in hexanes and filtered through a plug of silica gel. The silica gel was rinsed with 40% EtOAc in hexanes. The crude aldehyde solution was concentrated using a rotary evaporator and the crude aldehyde was used without further purification.

To as solution of diisopropylamine (15 μL, 0.11 mmol) in THF (1.1 mL) at 0 °C was added *n*-butyllithium (2.4 M in hexanes, 40 μL, 0.097 mmol). The reaction was stirred at 0 °C for 20 min before cooling to -78 °C. Methyl acetate (8.5 μL, 0.11 mmol) was then added to reaction and the reaction was stirred at -78 °C for 15 min. A solution of crude aldehyde dissolved in THF (0.3 mL) was then added dropwise to the reaction. The vial containing the aldehyde solution was rinsed with additional THF (0.1 mL) which was added dropwise to the reaction. The reaction was stirred at -78 °C for 30 min before warming to 0 °C and stirring for 30 min followed by warmed to room temperature and stirring for an additional 30 min. The reaction was poured into pH 7 phosphate buffer and diluted with DCM. The layers were separated and the aqueous phase was extracted three times with DCM and once with EtOAc. During the extraction, the resulting emulsion mixture was filtered through Celite® to separate layers. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was initially purified via silica gel flash chromatography (25% EtOAc in hexanes). The impure material was further purified via silica gel flash

chromatography (30% EtOAc in hexanes) to yield 15.0 mg of product as a colorless oil (38% yield over 2 steps). ^{1}H NMR (400 MHz, C_6D_6) δ 7.34 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H), 6.17 (dd, *J* = 9.8, 6.0 Hz, 1H), 5.84 (dd, *J* = 9.8, 0.9 Hz, 1H), 5.62 (ddd, *J* = 7.9, 5.8, 2.2 Hz, 1H), 4.31 (ddd, *J* = 8.4, 5.0, 3.5 Hz, 1H), 3.50 (s, 3H), 3.05 (dd, *J* = 9.3, 2.1 Hz, 1H), 2.82 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.66 (dd, *J* = 13.4, 9.0 Hz, 1H), 2.17 – 1.97 (m, 3H), 1.85 (dt, *J* = 14.2, 5.4 Hz, 1H), 1.79 (s, 3H), 1.72 – 1.62 (m, 1H), 1.55 – 1.38 (m, 1H), 1.37 – 1.16 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.69 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 170.0, 162.9, 149.1, 141.6, 129.5, 128.6, 126.2, 121.1, 85.6, 77.3, 71.5, 61.3, 41.9, 39.5, 38.4, 37.9, 34.5, 20.7, 20.6, 12.6, 10.9, 10.6. HRMS calc *m/z* $[C_{24}H_{34}O_5 + Na]^+$: 425.2298, found: 425.2246.



5.14

(*5R,6R*)-5-Ethyl-6-((*2R,3S,4R,5S*)-2-hydroxy-4-methoxy-3,5-dimethyl-6-phenylhexyl)-5,6-dihydro-2*H*-pyran-2-one (5.14). To a solution of lactone **5.33** (13.6 mg, 33.8 μmol) in MeOH (0.27 mL) was added HCl (3 M in MeOH, 50 μL, 150 μmol). The reaction was heated to 60 °C and stirred for 19 h. The reaction was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ and extracted three times with DCM and once with EtOAc. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were removed using a rotary evaporator. The crude material was initially purified via silica gel flash chromatography (40% EtOAc in hexanes). The

impure material was further purified via silica gel flash chromatography (45% EtOAc in hexanes and 5% to 12.5% EtOAc in DCM) to yield 5.0 mg of product as a white solid (41% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.41 – 7.25 (m, 2H), 7.19 (ddd, *J* = 6.2, 3.2, 1.8 Hz, 3H), 7.01 (dd, *J* = 9.8, 5.9 Hz, 1H), 5.97 (dd, *J* = 9.8, 0.9 Hz, 1H), 4.71 (dt, *J* = 9.2, 3.7 Hz, 1H), 4.30 – 4.11 (m, 1H), 3.51 (s, 3H), 3.14 – 3.01 (m, 2H), 2.81 (dd, *J* = 13.3, 4.7 Hz, 1H), 2.39 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.36 – 2.25 (m, 1H), 2.18 – 2.00 (m, 1H), 1.84 (tt, *J* = 7.0, 6.1 Hz, 1H), 1.78 – 1.61 (m, 3H), 1.55 – 1.40 (m, 1H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.96 (7, *J* = 7.5 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 164.8, 151.3, 141.5, 129.7, 128.8, 126.4, 121.2, 91.0, 78.3, 67.9, 61.8, 41.0, 40.0, 39.6, 38.7, 37.2, 21.4, 15.0, 12.3, 11.3. HRMS calc *m*/*z* $[C_{22}H_{32}O_4 + Na]^+$: 383.2193, found: 383.2095. 99% pure by HPLC analysis.

CHAPTER 7 BIBLIOGRAPHY

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